PHARMACOKINETICS OF ANTIBIOTICS IN ADULTS WITH MAJOR BURNS

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Abstract

Patients with major burns experience pathological changes which have been shown to influence the pharmacokinetics of antibiotics. Subsequently it has been demonstrated that conventional doses of some antibiotics given to patients with major burns may result in sub-therapeutic serum concentrations. The aim of this thesis was to identify antibiotics used to treat infection in critically ill patients with burns, and to develop dosage guidelines for those where data is lacking. A survey of antimicrobial use in burns centres in the UK was undertaken, leading to the identification of five antimicrobials to be studied further. Published pharmacokinetic values for gentamicin were used to develop dosage guidelines for extended dose administration. With vancomycin, current dose recommendations were reviewed for their appropriateness. Three more antimicrobials were identified where little or no pharmacokinetic data were available for patients with burns; meropenem, linezolid and colistin. A patient study was therefore set up where serum samples at steady state were collected from patients enabling the calculation of pharmacokinetic data. These were related to pharmacodynamic principles in order to propose dose recommendations.

With all three antimicrobials, serum concentrations were sub-therapeutic in some of the patients. For meropenem it is proposed that, for younger adults with evidence of abnormally high creatinine clearances, double the normal recommended total daily dose should be given. With linezolid, it is proposed that minimum inhibitory concentration measurements are used whenever possible in order to determine the required serum concentrations, and that more frequent initial dosing (an increase from two to three times a day) should be considered for younger patients with high creatinine clearance values. For colistin, a starting dose of 50% higher than the usual maximum is proposed for patients without evidence of renal impairment or low body-weight.

This thesis further confirms that the pharmacokinetics of antibiotics may be altered in patients with severe burns. Application of the dose recommendations may reduce morbidity and mortality in these critically ill patients.
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Preface

To understand the pharmacokinetics of antibiotics in burns patients, it is necessary to have an understanding of burn injury, infections and pharmacokinetics, as well as the individual drugs that have been selected to be studied. For this reason Chapter 1 of this thesis gives an overview of a typical patient with burns including both the pathophysiological changes that occur when a burn is sustained, and also the problem of infection in the burns patient. It will then focus on why the pharmacokinetics of drugs may be different in severely burned patients and the significance of this for antimicrobial therapy. To illustrate the principles described a semi-fictional case is then presented, followed by the aims and objectives of this thesis. It should be noted that references in this chapter generally date up to 2002, when the PhD was commenced, although where there have been any significant developments since then, the relevant papers are highlighted.

Chapter 2 presents the findings of two surveys regarding antimicrobial therapy in burns centres in the UK. The first was undertaken in 2001 to help with the identification of which antimicrobials required further investigation. The second, in 2009, gives an up-to-date picture of current treatment choices, so indicating the relevance of the work undertaken.

Chapter 3 describes the methodology for a clinical pharmacokinetic study of three antibacterial agents where there is little or no pharmacokinetic data. The chapter includes the laboratory work necessary to implement the study.

The next 3 chapters examines of the three antibiotics in detail, covering analysis of the pharmacokinetic data collected and the proposal of dosing models for each. As with Chapter 1, the papers discussed in the introduction to each of these chapters generally date up to 2002, with later references being included in the discussion.
Chapter 7 and 8 uses published data and local audit data of two further antibacterial agents, gentamicin and vancomycin, to review current guidance in patients with burns and make recommendations where required.

The final chapter reviews the aims and objectives of the thesis, and uses data from the previous chapters to achieve the final objective.
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There are three Duncans I would like to thank. My husband Duncan has not only been able to offer me his clinical pharmacy knowledge at times, but has supported and encouraged me through the last ten years. Secondly Duncan Livingstone was my manager at the commencement of the thesis and without his support I would not have been able to start the work. The third Duncan is my brother, who along with my sister, Lucy, has provided moral support over
the years. I am also indebted to my father, Tom, for so many things, but not least for the time he spent proof-reading this thesis.

My final thanks go to my three wonderful children Jude, Siân and Flynn McRobbie, who have made the work undertaken in this thesis feel all the more worthwhile.
Author’s declaration

I declare that the research contained in this thesis, unless otherwise formally indicated within the text, is the original work of the author. The thesis has not previously been submitted to this or any other university for a degree, and does not incorporate any material already submitted for a degree.
Chapter 1. Introduction

1.1. Burn Injury in the UK

Approximately a quarter of a million people in the UK every year experience an injury due to a burn. Of these, about 175,000 will visit an accident and emergency department and about 13,000 are admitted to hospital. One in thirteen of these will have severe burns and whilst the chances of survival from a severe burn have improved steadily over the last 25 years, in the UK there are still over 300 people who die every year from their injury (NCBR 2001).

The injuries from a burn may be multiple. In addition to physical problems such as shock, pain, infection and multi-organ failure, there are psychological issues such as post-traumatic stress disorder and dealing with disfigurement. Additionally there are often social problems such as rehousing after a house-fire.

In a review of patients admitted to hospital with burns in four counties in Eastern England in 1994 and 1995 (Wilkinson 1998), approximately two-thirds of patients were male. The age group that sustained the most burns were the 15 to 64 year olds (Figure 1.1a). This wide range age group accounted for 54% of all injuries, an average of 1.08% per age year. However, children in the 0 to 4 year age range accounted for 29% of all injuries, an average of 5.8% per age year, indicating that young children were most likely to sustain a burn. Burns were most commonly sustained to the wrist and hand, followed by lower limbs (Figure 1.1b), with only 1% of patients sustaining burns on multiple sites.
Figure 1.1 Age and location of burns in patients in Eastern England in 1994/5. Adapted from Wilkinson (1998)

Figure 1.1a shows that patients in the age range of 15 to 64 years age group most commonly sustained a burn. However almost one-third of the patients were in the narrow age range group of 0 to 4 years. It can be seen from figure 1.1b that burns to the wrist and hands were most common, with only 4% of all injuries being multiple sites.

The chances of an adult surviving a burn are known to decrease with increasing age and with increasing total burn surface area (Smith et al. 1994). Other factors have been associated with mortality following a burn injury including the presence of inhalation injury (Smith et al. 1994), wound sepsis and septicaemia (Bang et al. 1998), and pre-existing medical conditions and depth of burn.
Several models have been used to predict the likelihood of surviving a burn injury. One of the earliest (Bull and Fisher 1954) used curves to predict the mortality rate, according to the burn surface area and the age of the patient. This was later adapted as a grid (Bull 1971), where the probability of mortality (between 0 and 1) could be read off a chart using the age and total body surface area (TBSA) burn. (The latter is usually estimated by using a Lund and Browder Chart – see Section 1.2.2.) Another early model proposed that the likelihood of mortality (expressed as a percentage) could be calculated by adding the age and the total body surface area burn (Baux 1961). An adaptation, the Baux index, is still in use in adults where if a score is over 100, the prognosis is thought to be poor (Pereira, Murphy and Herndon 2004). Young patients are excluded from this model, as the effect of age on mortality is thought to be minimal at the age of 21 (Pruitt, Goodwin and Mason Jr 2002). Another scoring system assigns points according to the risk factors (Tobiasen, Hiebert and Edlich 1982b). This system is known as the Abbreviated Burn Severity Index (ABSI) and is shown in Table 1.1. In this system the heaviest weighting is assigned to TBSA burn, then age, and the least weighting to each of gender (female), inhalation injury and full-thickness burn.

In 1998 another model was proposed (Ryan et al. 1998). In this there are three risk factors; age more than 60, burn over 40% TBSA and the presence of an inhalation injury, and predicts a 0.3% mortality for no risk factors, a 3% mortality for one, a 33% mortality for two, and a 90% mortality for all three risk factors. Whilst this is simpler than the ABSI, it does have a cut off point and it is likely that it is less accurate when the TBSA burn and age are near to the risk factor values. Therefore a model using continuous ranges may be more accurate.
<table>
<thead>
<tr>
<th>Gender</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 20</td>
<td>1</td>
</tr>
<tr>
<td>21 - 40</td>
<td>2</td>
</tr>
<tr>
<td>41 - 60</td>
<td>3</td>
</tr>
<tr>
<td>61 - 80</td>
<td>4</td>
</tr>
<tr>
<td>81 - 100</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Presence of inhalation injury</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full-thickness burn sustained</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TBSA</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 10</td>
<td>1</td>
</tr>
<tr>
<td>11 - 20</td>
<td>2</td>
</tr>
<tr>
<td>21 - 30</td>
<td>3</td>
</tr>
<tr>
<td>31 – 40</td>
<td>4</td>
</tr>
<tr>
<td>41 – 50</td>
<td>5</td>
</tr>
<tr>
<td>51 – 60</td>
<td>6</td>
</tr>
<tr>
<td>61 – 70</td>
<td>7</td>
</tr>
<tr>
<td>71 – 80</td>
<td>8</td>
</tr>
<tr>
<td>81 – 90</td>
<td>9</td>
</tr>
<tr>
<td>91 - 100</td>
<td>10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total Score</th>
<th>Burn Threat to life</th>
<th>Probability of Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 – 3</td>
<td>Very Low</td>
<td>0.99</td>
</tr>
<tr>
<td>4 – 5</td>
<td>Moderate</td>
<td>0.98</td>
</tr>
<tr>
<td>6 – 7</td>
<td>Moderately severe</td>
<td>0.8 – 0.9</td>
</tr>
<tr>
<td>8 – 9</td>
<td>Serious</td>
<td>0.5 – 0.7</td>
</tr>
<tr>
<td>10 – 11</td>
<td>Severe</td>
<td>0.2 – 0.4</td>
</tr>
<tr>
<td>12 - 13</td>
<td>Maximum</td>
<td>≤ 0.1</td>
</tr>
</tbody>
</table>

Table 1.1 Abbreviated Burn Severity Index (ABSI). Adapted from Tobiasen et al (1982b)

With the ABSI, a score is assigned to each risk factor. A 45-year old (score 3) woman (score 1) with no inhalation injury (score 0), but a 35% TBSA flame burn (score 4), of which some was full-thickness (score 1) would have a score of 9.
Therefore the threat to her life is serious and the probability of survival for her is 0.5 to 0.7.

Over the past few decades, the chances of survival following burn injury have improved (Lionelli et al. 2005; Vehmeyer-Heeman et al. 2007). Whilst the Baux index has continued to be used (Pavoni et al. 2010) more models of differing complexity have also been proposed (Gomez et al. 2008; McGwin et al. 2008; Blot et al. 2009; Galeiras et al. 2009; Osler, Glance and Hosmer 2010). All of these have age and TBSA as major prognostic factors. It has also been proposed that the APACHE II score, a measure of severity of illness used in other kinds of critically ill patients, may be a useful tool for the prediction of mortality in burns patients (Tanaka, Shimizu and Hirabayashi 2007; Moore et al. 2010). Consensus at the Queen Victoria Hospital, the site of this study, is that this is not the case and it is not used (personal communication with S.Booth). A recent analysis of deaths at this site indicated that mortality rates correlated with levels indicated by the ABSI, Baux and Bull models, although no model was shown to be superior to the others (Booth and Vorster 2009).

1.2. Classification of Burns

Burn severity is assessed by burn size, depth and location.

1.2.1 Burn Depth

Burn depth in the UK is classed as superficial, dermal, deep dermal or full thickness (Figure 1.2). Dermal and deep-dermal are also known as “partial thickness”. When assessing the burn, only partial and full-thickness burns are considered significant. Superficial burns are also sometimes referred to as first degree burns, dermal and deep dermal as second degree burns, and full-thickness as third degree burns.
Figure 1.2. Skin structure and depth of burn (produced by Rostislav Shevchenko)

Figure 1.2 illustrates how the older way of describing the depth of burn by the “degree” relates to the current method of superficial, dermal, deep dermal and full thickness. Dermal and deep dermal are also referred to as “partial thickness”.

The skin is made up of two layers. The epidermis, the outer layer, is made up of several layers of epidermal cells, with the outermost being dead cornified cells. The main purpose of this layer is to protect against the environment. Burns to just to this epidermis layer are called superficial burns.

The dermis underneath is much thicker than the epidermis, and is responsible for the elasticity of the skin. Together with the epidermis it controls the loss of body fluids and heat, by acting as a barrier, but also through evaporation of sweat and vasodilation when cooling is required. Burns to this layer are either dermal (also known as superficial dermal) or deep dermal depending on the depth of the injury. Most of the dermis is made up of collagen and elastic fibres, and contains the microcirculation i.e. arterioles, venules and capillaries. This layer also contains sweat glands, sebaceous glands and hair follicles, which are
lined with epidermal cells. Additionally there are nerve endings which detect touch, pressure, pain, cold and heat. Beneath the dermis is a subcutaneous fat layer, and burns that extend to this depth, or deeper are known as full-thickness (Arturson 1996; Williams 2002).

Burn depth can be difficult to estimate (Table 1.2). A needle pin-prick can be used to differentiate between partial- and full-thickness burns. In the latter, the patient feels no sensation to pin-prick due to loss of nerve endings. These burns tend to have a brown, hard and leathery eschar. A burn that gives no sensation to pin-prick but has a mottled red and white appearance is more-likely to be deep-dermal. With this depth of wound, pressure sensation may remain, due to survival of deeply-situated pressure receptors. The cause of burn can also help with assessment of the depth; full-thickness burns may be caused by blazing clothing or contact burns, whereas flash burns and scalds are more likely to be partial thickness (Marsden 1996; Pape, Judkins and Settle 2000; Williams 2002).
<table>
<thead>
<tr>
<th>Burn Depth</th>
<th>Characteristics</th>
</tr>
</thead>
</table>
| **Superficial**    | • Skin is dry and intact and painful  
                     • Blanches under pressure  
                     • Minimal tissue damage  
                     • Usually no blisters |
| **Superficial Dermal (superficial partial thickness)** | • Blisters immediately  
                     • Wound bed, normally pink/red  
                     • Moist with moderate exudate  
                     • Brisk capillary refill  
                     • Very painful  
                     • Sensitive to pain, air, and temperature |
| **Deep Dermal (partial thickness)** | • Red/ Pale white creamy wound bed  
                     • If blisters present, easy to separate, loose epidermis  
                     • Sluggish capillary refill  
                     • Slight pain but mostly insensate  
                     • Sensitive to deep pressure but not pinprick |
| **Full Thickness** | • White, cream, or cherry red wound bed  
                     • Black/brown leathery eschar  
                     • Minimal pain, if any  
                     • Thrombosed vessels may be visible  
                     • Insensate |

**Table 1.2. Guide to assessment of burn depth** (reproduced from Queen Victoria Hospital Burns Handbook by kind permission B. Dheansa)

Burn depth can be difficult to assess. This table gives a guide to help determine the depth of burn.
Assessment of burn depth may be aided by laser doppler imaging (Banwell et al. 1999). The depth of burn is important as it dictates management. Epidermal and superficial dermal burns will heal by re-epithelialisation from epidermal cells at the edge of the wound, or from structures such as the hair follicles and sweat glands. Deep-dermal and full-thickness burns cannot heal by re-epithelialisation, as the hair-follicles and sweat glands have usually been destroyed. Instead the wound will contract so that it will eventually meet, which can result in gross deformities and limited movement. To avoid this occurring, surgical intervention is required (see 1.4.2).

1.2.2 Burn size

The size of a burn is usually expressed as the percentage of the total body surface area (TBSA). In the UK it is most often assessed by using the Lund and Browder chart (Figure 1.3). This is completed by shading in the areas on a diagram of the front and back of a whole body that are assessed to be either partial-thickness (conventionally a single hatch pattern) or full-thickness (cross hatch). The percentage area burned for areas of the body can then be estimated and added together to give an estimate of the total percentage burn area. A completed Lund and Browder chart is shown as part of the case presentation in Section 1.9.
Figure 1.3. Lund and Browder Chart to assess the size of the burn (by kind permission of Smith and Nephew)

The Lund and Browder chart is used to estimate the total percentage area burned. Numbers on the areas of the body indicate the percentage if all of that area is burned. For example if one side of a hand was totally burned, then this would be estimated to be a $1\frac{1}{2}\%$ burn. For some areas, such as the head, the area varies according to age which is indicated by letter A, B and C; in a one year old if half of the head was burned, this would be estimated to be a $8\frac{1}{2}\%$ burn, whereas the same area in an adult would only be $3\frac{1}{2}\%$. The estimated percentage burn for each part of the body is recorded according the depth (PTL = partial thickness, FTL = full thickness) and then figures in each column added to give the total percentage burn for each depth. These two values can then be added together to give the total percentage body surface area burn.
1.2.3 Burn location and cause

The areas of the body where the burns are sustained also need to be described. An example of a burn description would therefore be a 40% TBSA flame burn, mixed depth (i.e. full and partial thickness) to the chest, back, abdomen, right arm and right leg.

The description is important as it will help to determine the initial management of the patient. Those with large percentage TBSA burns, or deep dermal or full-thickness burns to areas such as the hands or face will require the supervision of a specialist burns unit or centre (see Table 1.3). Generally this will mean either transfer to the unit or centre, or out-patient management there. Where there are other traumatic injuries or the treatment is that of comfort care only, patients may remain elsewhere, but receive advice from the specialist burns service.
<table>
<thead>
<tr>
<th>Age</th>
<th>Under 5 years or over 60 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site</td>
<td>Face, hands, perineum or feet (with dermal or full-thickness loss) Any flexure, particularly the neck or axilla, or any circumferential dermal or full-thickness burn to the limbs, torso or neck</td>
</tr>
<tr>
<td>Inhalation injury</td>
<td>(with or without a burn)</td>
</tr>
<tr>
<td>Cause of injury</td>
<td>Chemical (&gt;5% TBSA)</td>
</tr>
<tr>
<td></td>
<td>Ionizing radiation</td>
</tr>
<tr>
<td></td>
<td>High pressure steam</td>
</tr>
<tr>
<td></td>
<td>High tension electricity</td>
</tr>
<tr>
<td></td>
<td>Hydrofluoric acid (&gt;1% TBSA)</td>
</tr>
<tr>
<td></td>
<td>Suspicion that non-accidental</td>
</tr>
<tr>
<td>Size (dermal or full-thickness)</td>
<td>Under 16 years &gt; 5% TBSA</td>
</tr>
<tr>
<td></td>
<td>Adult &gt; 10% TBSA</td>
</tr>
<tr>
<td>Existing conditions</td>
<td>Cardiac limitation and MI within 5 years</td>
</tr>
<tr>
<td></td>
<td>Respiratory Limitation of exercise</td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
</tr>
<tr>
<td></td>
<td>Pregnancy</td>
</tr>
<tr>
<td></td>
<td>Immunosuppression</td>
</tr>
<tr>
<td></td>
<td>Hepatic impairment; cirrhosis</td>
</tr>
<tr>
<td>Associated injuries</td>
<td>Crush injuries</td>
</tr>
<tr>
<td></td>
<td>Fractures</td>
</tr>
<tr>
<td></td>
<td>Head injury</td>
</tr>
<tr>
<td></td>
<td>Penetrating injuries</td>
</tr>
<tr>
<td>Vesiculobullous disorder (non-burn) e.g.</td>
<td>Any &gt; 5% TBSA</td>
</tr>
<tr>
<td></td>
<td>Epidermolysis bullosa</td>
</tr>
<tr>
<td></td>
<td>Staphylococcal scalded skin syndrome (Ritter’s)</td>
</tr>
<tr>
<td></td>
<td>Stevens-Johnson syndrome</td>
</tr>
<tr>
<td></td>
<td>Toxic epidermal necrolysis (Lyell’s)</td>
</tr>
</tbody>
</table>

**Table 1.3 Guide to referral to a specialist burns unit / centre. Adapted from NCBR (2001)**

The National Burn Care Review developed guidance for health care professionals as to when to refer to a specialist burns unit or centre. If any of the factors listed apply, referral should be made.
1.3 Pathophysiology

The body responds to burn injury both locally at the burn wound and systemically. A large burn, of about 30% TBSA or higher, does not only cause damage to the skin, but affects many organs throughout the body, resulting in complex pathological changes (Pape, Judkins and Settle 2000; Treharne LJ 2004). Physiologically, there are two phases that occur following a large burn injury; the acute phase and the hypermetabolic phase.

When a burn is sustained, vasodilatation occurs at the wound site in order to dissipate the heat from the burn. At the same time there are increases in capillary permeability in the tissues affected, but not destroyed, by the burn. The vasodilatation of the wound, together with the capillary leak, results in increased flow of fluids and proteins into the interstitial space, which exceeds the capacity of the lymphatic drainage system. As a result, there is oedema at the burn wound site. The damage to the skin cells also causes the release of inflammatory mediators such as thromboxanes, prostaglandins and cytokines leading to a local inflammatory response (Pape, Judkins and Settle 2000).

The acute phase lasts for the first 48 hours after the injury. When a large burn is sustained, more inflammatory mediators are released than with a small burn. Numbers are sufficient to reach the circulation and cause a systemic effect. During this phase, the capillary leak affects the whole body, including unburned skin, and organs such as the lungs, liver and kidneys (Pape, Judkins and Settle 2000). Fluid and plasma proteins, such as albumin, are lost from the intravascular space through the leaky capillaries. For a patient with extensive burns of greater than 50% TBSA, unless large volumes of intravenous fluid are administered, blood volume may be depleted by one-third after three or four hours. With such depletion, the patient will be in severe shock, which is life-threatening (Pape, Judkins and Settle 2000).
After approximately 48 hours, the hypermetabolic phase commences, which can last for weeks or months. Systemic effects of the inflammatory mediators cause an increase in metabolic rate, resulting in a rise in the patient’s core body temperature (Wolfe, Herndon and Jahoor 1987), and a greater cardiac output (Aikawa, Martyn and Burke 1978). This increases blood flow to organs and tissues. The raised metabolic rate (approximately double of a non-burned patient) is thought to be due to increased substrate cycling involving adenosine triphosphate (ATP) (Demling 1985; Wolfe, Herndon and Jahoor 1987).

Of particular significance to pharmacokinetics, is the effect of hypermetabolism on renal and hepatic function. Renal function is often expressed as creatinine clearance, with a low value indicating renal impairment. One study measured a significantly greater creatinine clearance in twenty patients with burns, measured between the fourth and the 35th post-burn day, compared with eight non-burn subjects (p < 0.02) (Loirat et al. 1978). The increase in creatinine clearance may be due to hypoproteinaemia, increased prostaglandin synthesis and / or increased renal blood flow (Bonate 1990).

As with the kidney, blood flow through the liver is significantly increased in patients with burns compared with those without (Wilmore, Goodwin and Aulick 1980). Despite this increase in blood flow, severe burns may cause impairment of enzyme activity. This was demonstrated by measurement of a significantly lower renal excretion of D-glucaric acid (a metabolite correlating with drug-metabolising activity) in patients with burns compared with healthy volunteers (Ciaccio and Fruncillo 1979). Decreases in cytochrome P-450 activity and all related oxidation, reduction and hydroxylation reactions have been documented, but other drug metabolism pathways, such as conjugation, are thought to be unaffected (Weinbren 1999).

The hypermetabolic phase is also characterised by oedema formation. This is both in the interstitium and, to a lesser extent, inside cells (Kinsky et al. 1998). The interstitial oedema is primarily due to hypoproteinaemia; because capillary leak has resulted in plasma proteins moving from the intravascular space into the interstitium, the osmotic pressure of the proteins moves water out of the
capillaries. This is aided by an increase in water permeability of the interstitial space (Demling 1987). Albumin levels are further lowered in the hypermetabolic phase as the liver shifts from the synthesis of proteins such as albumin, pre-albumin and transferrin, to other proteins such as α1-acid glycoprotein and fibrinogen, in order to promote immune function, coagulation and wound-healing (Jeschke 2002).

Pathophysiological changes also cause a suppressed immunological response, as demonstrated by prolonged survival of human skin allografts (Ninnemann, Fisher and Frank 1978) and suppression of delayed hypersensitivity reactions (Casson et al. 1966). This is due to a complex series of changes, triggered within two hours of injury by two cascades; the arachidonic acid cascade and the inflammatory response cytokine cascade. As a result of these cascades, there are alterations in the functions of lymphocytes, macrophages and neutrophils, as well as translocation of bacteria and bacterial products. These changes interfere with the biological efficiency of the body to fight invading pathogens, and may cause cell damage and cell death (Munster 2002).

1.4. Overview of treatment of burn injury

1.4.1. Circulation

Due to leaky capillaries, adults with burns of at least 15% TBSA and children of at least 10% TBSA require large volumes of intravenous fluid in the acute phase to maintain fluid volume in the vascular compartment and prevent burn shock occurring. The most appropriate choice of fluid and the volume required has been proposed by several different researchers over the last century. For many years in the UK, the Muir and Barclay formula was the most widely adopted, which most recently used a colloid1 such as albumin (Muir and Barclay 1974). However, in the late 1990s a systematic review of randomised controlled trials in critically ill patients with hypovolaemia, burns, or hypoalbuminaemia comparing the administration of albumin or plasma protein fraction with the

---

1 An intravenous solution containing finely dispersed particles. These are used in therapy because the particles may be too large to pass through capillaries (that are not leaky), thus maintaining an osmotic (oncotic) pressure, and helping fluid to remain in the intravascular compartment.
administration of crystalloid\(^2\) solution, raised concerns that colloids may increase mortality (Roberts 1998). As a result, UK burns units changed to using the Parkland Formula, which was already in use in the USA (Baxter and Shires 1968). This uses Hartmann’s solution (a crystalloid solution that is isotonic with blood), selected as it is more physiologically similar to plasma than other crystalloids. With this, a volume of 4ml/kg/\%TBSA burn is administered over the first 24 hours post-burn. Half of this is given over the first eight hours and the rest over the next sixteen hours. This formula is only a guide, and the infusion rate is adjusted according to the patient’s needs, monitored by the haematocrit and the urine output. The formula is amended for children to account for their different body surface area to weight ratio.

In the hypermetabolic phase, patients may also suffer circulatory problems, as a result of the systemic inflammatory response syndrome (SIRS). Patients are diagnosed as having SIRS if they have at least two of the following (Bone et al. 1992):

- High (>38\(^\circ\)C) or low (<36\(^\circ\)C) body temperature
- Heart rate of greater than 90 beats per minute
- Respiratory rate of at least 20 breaths per minute or partial pressure of carbon dioxide in the blood (PaCO\(_2\)) of less than 32mmHg
- High (>12,000/μl) or low (<4000/μl) leukocyte count, or at least 10% immature forms

Refractory hypotension may develop, which requires the use of inotropic drugs and appropriate fluid therapy. Burns units may also test for cortisol levels and if low, administer a short course of the corticosteroids, hydrocortisone (cortisol) and fludrocortisone (a mineralocorticoid) (Annane et al. 2002). At its worst, SIRS may lead to shock and multi organ failure. When SIRS occurs with the presence of infection, it is defined as sepsis. Burns patients, in particular children, are thought to be at risk of developing toxic shock syndrome due to

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\(^2\) An intravenous fluid of water and glucose and / or electrolytes that are dissolved in the solution.
bacterial toxins, symptoms of which include severe hypotension (Frame et al. 1985). Treatment is with antibiotics and fluids.

1.4.2. Skin

Unhealed wounds increase the risk of burns patients developing sepsis. Additionally patients will lose fluids, electrolytes and proteins through the open burn wound. Therefore the mainstay of burns treatment is surgery to close wounds as soon as possible. Additionally wounds that take more than 10 days to heal are at increased risk of hypertrophic scar formation (Deitch, Wheelahan and Paige Rose 1983). Since 2002, it has become routine practice not to undertake surgery on patients with scalds where healing is predicted to occur in less than 3 weeks. This followed evidence from a study in 337 children (Cubison, Pape and Parkhouse 2006) which found there was a low risk of hypertrophic scar formation in scalds that healed before 21 days.

There is a general consensus that early total excision of full-thickness and deep dermal burns, i.e. removal of all of the burn eschar (a slough or piece of dead tissue (scab) that is cast off from the surface of the skin), should be undertaken if possible. This occurs in the first few days after the burn, and with large burns may be a series of operations under general anaesthesia. As a result, bacterial colonisation of the wound is thought to be lessened, and there is evidence to suggest that this approach reduces mortality, at least in some sub-groups of patients (Herndon et al. 1989; Huang et al. 2001). If there is a limited supply of suitable unburned skin for skin-grafting, alternative wound cover is required. This is usually an allograft (cadaveric skin) which, because of the patient’s suppressed immune response, will last longer than would normally be expected. As it will eventually be rejected, it will need to be replaced with the patient’s own skin (autograft), or more allograft if sufficient autograft is not yet available. The alternative to allograft is a synthetic skin substitute. This is only suitable for use in some areas of the body, and the burn wound will still require eventual grafting with autograft. However the autograft will be thinner than would normally be required for grafting a deep dermal or full-thickness burn (Muller, Ralston and Herndon 2002).
Some patients may be too infirm to tolerate aggressive surgery. In such cases, it is possible to wait for spontaneous eschar separation and then undertake skin grafting, but this is associated with pain, severe metabolic derangements, sepsis and prolonged length of stay in hospital (Muller, Ralston and Herndon 2002). Alternatively, staged surgical wound closure could take place, which is a less aggressive approach than early total excision. Here, different wounds are excised in stages at approximately weekly intervals, and are closed using an autograft. This gives more time for donor areas to heal and be used again (Monafo and Bessey 2002).

For burns on the face, the donor site areas of choice are the scalp or the back of the neck, as they are the best match to facial skin colour. Otherwise whenever possible, donor sites are selected from areas that are hidden by clothing, such as the thigh or buttocks. With large burns some unusual areas may need to be used, such as the axillae, back, scrotum or groin. Split skin grafts (epidermis and some of the dermis) are generally used, but areas such as the eye-lid may require a full-thickness skin graft (epidermis and all of the dermis) (personal communication with B.Dheansa, Consultant Burns Surgeon at the Queen Victoria Hospital). An alternative method to increase the availability of autologous skin on patients with large burn areas is the use of cultured epithelial cells (Brychta et al. 2002). This method, first reported for use in patients with burns in 1981 (O'Connor, Mulliken and Banks-Schlegel 1981), uses epithelial cells taken from a small skin biopsy. The cells are placed in cultured medium, so that they can grow into colonies. Initially the cells were applied as sheets but are now usually made up into a suspension and delivered by aerosol to debrided burn wounds and sometimes also to donor skin graft areas (Stark et al. 1995). In a retrospective audit Wood et al (2006) showed that there was a reduction in surgical intervention and total length of stay / %TBSA burn when practice moved from using the sheets to the aerosol.

Grafts may fail if the colonisation of wounds develops into local infection. Loss of graft may also be caused by the scratching of itchy areas, weight-bearing, rubbing or poor circulation (Klasen 1996b).
Wound care is a major part of patient care. Dressings are necessary to absorb burn exudate, provide wound protection and to decrease wound pain. Dressing changes occur as frequently as every day or two depending on the volume of exudate. General anaesthesia is not usually required for this, but an anaesthetist will often be present to administer intravenous analgesia and sedation.

Another major problem with burnt skin is the pain it causes the patient. Initially, acute pain is a problem, but this can develop into chronic pain. Other long-term problems with the skin include itching, keloid scarring, and disfigurement. Physiotherapy will be undertaken to maintain the range of movement and the occupational therapist will fit splints to prevent wound contractures, as well as pressure garments to reduce the extent of scarring.

1.4.3. Lungs

Respiratory complications occur in a large proportion of patients with severe burns, even in the absence of inhalation injury (Beeley and Clark 1996). They are the most common cause of death in hospitalised burned patients, usually due to respiratory tract sepsis (Shirani, Pruitt Jr and Mason Jr 1987), often as part of multi-organ failure (Marshall and Dimick 1983).

Patients who sustain an inhalation injury have a higher risk of mortality (Tobiasen, Hiebert and Edlich 1982a). Estimates of mortality vary between 34.7% (Tredget et al. 1990) and 47% (Darling et al. 1996), with mortality being most significant in burns > 15% TBSA (Darling et al. 1996). This may be because patients with burns over this size receive large volumes of intravenous fluids, necessary to prevent burns shock, but which may also increase pulmonary complications due to leaky capillaries allowing more fluid into the lungs.

There are many possible reasons that inhalation injury - with or without a burn - does so much damage to the lungs. These have been summarised as damage to the mucosal barrier, impaired mucociliary transport, activation of neutrophils,
release of oxygen-free radicals, increased microvascular permeability, and reduction in surfactant (Darling et al. 1996).

In the ventilated patient, chest physiotherapy is administered frequently to reduce oedema and remove foreign substances such as soot. If an inhalation injury is confirmed by bronchoscopy, an intensive short course of inhaled medicines are administered, for example every two hours. The choice of drug may vary between units, but will usually include at least one of; salbutamol (a beta-2 agonist to produce bronchodilation), normal saline (to flush out foreign substances), N-acetylcysteine and / or heparin³ (Desai et al. 1998; Vorster, Sim and Allen 1999). A recent retrospective study of 30 patients with smoke inhalation injury (Miller et al. 2009) showed a significantly lower mortality rate in patients who received N-acetylcysteine, heparin and a beta-2 agonist, compared with those who received only a beta-2 agonist, with a number needed to treat of 2.7.

Respiratory problems may be further worsened by burns to the head and neck area, as the presence of oedema and eschar can make it more difficult for the patient to breathe (Beeley and Clark 1996; Holm et al. 1999).

1.4.4. Kidneys

Acute renal failure (ARF) has been reported to complicate 14.6% of patients with a TBSA burn of greater than 10%. ARF in patients with burns has a poor prognosis, with reported mortality rates since 1990 of at least 80% (Davies, Evans and McGonigle 1994; Leblanc, Thibeault and Querin 1997).

In the first few days after a major burn injury, acute renal failure is a risk, due to hypovolaemia. However, since the introduction of administration of large volumes of intravenous fluids in the acute phase, this complication usually occurs at a much later stage, and is thought to be related to sepsis and multi-organ failure. The risk of developing ARF at this later stage is thought to be

³ Heparin and n-acetylcysteine are thought to be oxygen-free radical scavengers. In animal studies this combination has been shown to decrease the formation of fibrin casts and reduce peak inspiratory pressures (Desai et al. 1986)
greater if the patient also has an inhalational injury and the risk also increases with increasing TBSA burn (Holm et al. 1999).

1.4.5. Nutrition and blood

The gastro-intestinal tract is affected by burns. In burns of at least 20% TBSA, paralytic ileus occurs during the first 24 hours and gastroduodenal ulcers may develop (Rose and Jordan 1999). Feeding is commenced as early as possible, usually via an enteral tube, to reduce the risk of these occurring. Burns patients are at risk of gut stasis for several reasons, including use of opioid analgesics, immobility and as a consequence of the burn injury itself. Laxatives are administered routinely, and if there are signs that the patient’s naso-gastric feed is not being absorbed, gut-motility agents may be commenced.

The hypermetabolic state of the patient increases nutritional requirements and patients frequently develop abnormalities of glucose control, as well as irregularities in the metabolism of vitamins, minerals and trace elements. Should hyperglycaemia occur, a continuous intravenous infusion of insulin is administered. Hypokalaemia and hypomagnesaemia are common in severely burned patients and require supplementation, usually by the intravenous route. With sodium, hypernatraemia is more common than hyponatraemia, and a review of the sodium content of the fluids the patient is receiving is necessary. The cause is likely to be multi-factorial but is probably mainly due to increased free water loss through the burn wound, and increased respiration associated with pyrexia.

Despite aggressive enteral feeding, muscle-wasting can be a problem (Lund and Onarheim 1996) and physiotherapy is undertaken to improve muscle strength. Patients may receive immunomodulatory agents, such as glutamine, to counteract the effects of immunosuppression (Wischmeyer et al. 2001).

Patients with large burns may develop haematological problems. Nearly all of those with severe burns will have anaemia, with a low red cell count, caused by red cell destruction. Neutropenia, thrombocytopenia and disseminated intravascular coagulation may also occur (Sheridan and Pruitt 1996). Patients
are also at an increased risk of thromboembolic events compared with healthy individuals (Wibbenmeyer et al. 2003), due to venous stasis, endothelial injury and hypercoagulability. Patients should receive mechanical prophylaxis, such as antiembolic stockings, if the location of the burn allows this. Additionally, low molecular weight heparin is usually given subcutaneously once a day.

1.4.6. Psychological problems

The patient may require psychological support to cope with the burn injury for several possible reasons:

- The circumstances in which the burn occurred, including post-traumatic stress disorder
- The death of another person
- The disfigurement as a result of the injury.

In addition, help may be required for the patient’s family, especially in the case of a child where the parent may feel responsible for the injury occurring.

1.5. Infection

Infection is a major cause of death and illness in burns patients (Pruitt 1984; Weber and Tompkins 1993; Law, Blecher and Still 1994; Soltani, Zand and Mirghasemi 1998) and it has been estimated that as many as 75% of all deaths not due to the immediate burn injury are related to infection (Polk 1979; Pruitt 1984). Fry et al (1980) showed that infection is the most common cause of multiple organ system failure in trauma patients, and Marshall and Dimick (1983) reported a death rate of 75% in burns patients with multiple organ system failure due to sepsis. In a review of 529 patients with burns, Saffle et al (1993) showed that sepsis was present in 22 of 33 patients who died. Another study (Bang et al. 2002) compared data from patients treated from their earlier study (Bang et al. 1998) over the four year period up to May 1996 (group 1) and the four-year period from June 1996. Multiple organ failure as a consequence of septicaemia was the cause of death in 60.9% of the patients who died in group 1 and in 85.7% of those who died in group 2. More recently in a review of
175 adults with burns of at least 20% TBSA, but excluding those admitted for comfort care only (Fitzwater et al. 2003), 79 patients (45%) developed an infection. Nineteen patients survived the initial injury (i.e. at least 72 hours) but died later. Of these, the cause of death was considered to be secondary to sepsis in fourteen patients (74%) indicating little change in this rate since the 1970s.

1.5.1 Risk factors for infection

A patient with burns is at high risk of infection primarily because the burn wound provides a route of entry into the body, but also because of the patient’s immunocompromised state, mechanical ventilation, prolonged time in hospital, gastrointestinal translocation, invasive procedures and urinary catheterisation. The risk of developing burn wound infection depends on both patient factors such as age and size of burn, and microbial factors such as the type and density of microorganisms invading the wound (Table 1.4).
## Risk Factors

### Highest risk

**Patient Factors**

- Extent of the burn: > 30% TBSA, but risk increases as burn surface area increases further
- Depth of Burn: Full-thickness
- Age of the patient: Children and elderly
- Pre-existing illness: Diabetes, cardio-pulmonary disease, immunologic deficiencies, obesity, malnutrition
- Inhalation injury: Presence of injury
- Wound hydration: Moist wounds
- Wound temperature: Warmer temperatures
- Blood flow to wound: Impaired blood flow
- pH: Metabolic acidosis

**Microbial Factors**

- Density: > $10^5$ organisms per gram of tissue
- Motility: Motile strains
- Metabolic products: Endotoxins and Exotoxins

### Table 1.4 Risk factors for burn wound infection. Adapted from Pruitt (1984)

Patients with burns are at an increased risk of burn wound infection. Factors that increase the risk include size and depth of burn, the patient’s age and pre-existing illnesses, and wound factors. Additionally bacterial characteristics add to the risk factors.

### 1.5.2 Sites of infection

Infection in patients with burns commonly occurs in the wound and blood, as well as the respiratory and urinary tracts.

The burn wound provides ideal conditions for the growth of bacteria, such as the availability of nutrients, a moist environment and an ideal temperature. As a result, burn wounds are usually colonised with the patient’s resident commensal
flora, or with bacteria from exogenous sources such as staff, air and equipment (Sohal 1996). Colonised wounds of low bacterial numbers may not be a problem clinically, but when counts reach the order of $10^5$/g of tissue the patient may develop burn wound sepsis. Signs of a local infection include an infection in the adjacent unburned tissue, partial-thickness burn developing into full-thickness and sloughy wounds (Heggers and Robson 1986).

Septicaemia is usually caused by the passage of bacteria through the burn wound to the blood. The risk of respiratory tract infections is increased by mechanical ventilation and may be caused by bacterial translocation. Bacterial translocation to lymph nodes, liver, kidney, spleen and lungs has been demonstrated in burned sheep (Morris, Navaratnam and Herndon 1980), and an increase in bowel permeability has been demonstrated in burned patients (Ziegler et al. 1988). The risk of developing a urinary tract infection in burns patients is increased as most require urinary catheterisation.

Infections in burns patients may be difficult to diagnose, as many of the symptoms of an infection are shared with those of a major burn injury (See also Section 1.5.3). These include symptoms occurring during the hypermetabolic phase, such as increased temperature and tachycardia, and neutrophil count changes due to immunosuppression (Pruitt 1984).

1.5.3. Organisms commonly identified from burn wounds

The earliest organisms isolated from burn wounds tend to be Gram-positive organisms, such as staphylococci. In the latter part of the first post-burn week, Gram-negative organisms become dominant (Pruitt and Lindberg 1979) which may be from gut flora, the hospital environment and / or contamination from health care workers. A study of bacterial isolates from 600 wound swabs of burns patients in India (Revathi, Puri and Jain 1998) found that Pseudomonas spp was the most common (36%), followed by Staphylococcus aureus (19%), Klebsiella spp (16%), Proteus spp (11%), Enterococcus faecalis (9%), Escherichia coli (5%), Acinetobacter spp (1%) and others including beta-haemolytic streptococci, coagulase-negative staphylococci and diphtheroids. Similar findings were reported from a study in Italy (Donati et al. 1993) with
Psuedomonas aeruginosa being the most common isolate, followed by Staphylococcus aureus and Enterococcus spp. Less frequently reported pathogens included Klebsiella spp, Proteus mirabilis, Escherichia coli, Enterobacter cloacae, coagulase negative staphylococci, Acinetobacter spp. and Citrobacter spp. More recently Guggenheim et al (2009) reported that S.aureus (20.8%) was the most common organism isolated from patients with burns over a 20 year study period. This was followed by E.coli (13.9%) and P.aeruginosa (9.7%). There are also case reports of burn infection caused by Bacillus cereus (Attwood and Evans 1983). Toxic shock syndrome, which can be fatal and is more common in children with burns than adults, is thought to be most likely caused by toxins produced by S.aureus (Frame et al. 1985). Fungi may also cause infections (Sohal 1996).

Table 1.5 summarises commonly isolated bacteria according to their classification.

<table>
<thead>
<tr>
<th>Gram-positive cocci</th>
<th>Gram-positive rods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus spp.</td>
<td>Bacillus spp.</td>
</tr>
<tr>
<td>Streptococcus spp.</td>
<td>Diphtheroids</td>
</tr>
<tr>
<td>Enterococcus spp.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gram-negative aerobic rods</th>
<th>Gram-negative facultatively anaerobic rods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudomonas spp.</td>
<td>Escherichia coli</td>
</tr>
<tr>
<td>Acinetobacter spp.</td>
<td>Enterobacter cloacae</td>
</tr>
<tr>
<td>Stenotrophomonas spp.</td>
<td>Klebsiella spp.</td>
</tr>
<tr>
<td></td>
<td>Proteus mirabilis</td>
</tr>
<tr>
<td></td>
<td>Citrobacter spp.</td>
</tr>
</tbody>
</table>

Table 1.5 Classification of common organisms isolated from burn wounds

Initially after the burn occurs Gram-positive organisms only tend to be isolated from wounds, of which S.aureus is the most common. It is usually about five days before Gram-negative organisms, in particular P.aeruginosa, become dominant.
The symptoms of a burn wound sepsis may vary depending on whether it is caused by Gram-positive or Gram-negative organisms. Both are characterised by a high bacterial count, low blood pressure, decreased urinary output and decreased bowel sounds. However Gram-positive infections are also associated with a slower onset of symptoms, higher body temperatures and higher white cell counts (Heggers et al. 2002).

1.5.4. Infection Control

Numbers of bacteria in the wound should be kept to a minimum, as it is known that wound sepsis occurs when bacterial counts from colonised wounds reach approximately $10^5/g$ tissue. This then increases the risk of systemic infection (Heggers et al. 2002). Colonisation of the burn wound can be prevented or reduced by infection control measures from staff and visitors, and also maintaining a clean environment. Until wounds are surgically closed, topical antimicrobial therapy is applied to burn wounds (Klasen 1996a). In the UK, a commonly-used preparation Flammacereum®, a combination of silver sulphadiazine and cerium nitrate hexahydrate, is often the agent of choice. Other preparations may be used such as silver nitrate solution, sodium hypochlorite solution and mupirocin ointment.

Silver sulphadiazine has been used for many years and is particularly effective against *P. aeruginosa* (although resistance has been reported) and also against *E. coli*, *Enterobacter* spp, *Serratia marcescens* and *Candida albicans*. Silver sulphadiazine may not be as effective against *S. aureus* and some *Klebsiella* species (Heggers et al. 2002). It has the added benefit that it may relieve pain (Sharma, Wosornu and Paonaskar 1979) but when used alone it may delay wound healing (Stern 1989).

Cerium nitrate is effective against organisms such as *P. aeruginosa*, *S. aureus* and *Escherichia* spp (Burkes and McCleskey 1947), and is synergistic with silver sulphadiazine (Monafo et al. 1976). In addition to its antimicrobial activity, cerium nitrate has the added benefit that it hardens the burn eschar, so reducing the frequency of dressing changes (Scheidegger et al. 1992) and makes excision surgery easier (Koller and Orsag 1998). There is some
evidence to suggest that the use of cerium nitrate reduces mortality (Monafo et al. 1976) which may be due to the hard eschar preventing bacteria from colonising the wound. Alternatively it may reduce immunosupression, thought to be due to its prevention of the burn wound toxin reaching the systemic circulation (Kremer, Allgower and Graf 1981). Cerium nitrate can cause stinging on application (Monafo 1983) and there are rare reports of methaemoglobinemia (Monafo et al. 1976).

Prophylactic systemic antimicrobial therapy is usually given only peri-operatively, as continued prophylaxis may result in the development of bacterial resistance (Lilly and Lowbury 1978).

Wound infections without any systemic signs of infection are usually not treated with antibiotics. Instead, wounds are cleaned with an anti-bacterial solution, such as povidone iodine. They are then covered with an antibacterial cream, such as Flammacerium®, and redressed (personal communication with P.Gilbert, Consultant Burns Surgeon at the Queen Victoria Hospital).

1.6. Antibacterial therapy

If a patient develops systemic signs of infections, antibiotic therapy is commenced immediately. The choice of drug is often empiric, but may be guided by bacteria identified from recent wound cultures. Before treatment is commenced, samples are taken from sites such as the wound, blood, sputum and urine. Then if a patient is not responding to initial therapy, the antibiotic regimen may be altered to one based on the organisms identified from these samples and their reported susceptibilities.

Within each group of antibiotics, the spectrum of activity of antibacterials may differ for several reasons, including the ability to penetrate cell walls and resistance to bacterial enzymes. A brief overview follows of antibiotics that may be used to treat systemic infections in burns patients.
1.6.1. Aminoglycoside antibiotics

Aminoglycosides, such as gentamicin, inhibit protein synthesis by binding irreversibly to the 30S ribosomal subunit. The main effect of this is inhibition of translation of messenger RNA to protein. They are active against some Gram-positive and many Gram-negative organisms, but not against anaerobic bacteria. Aminoglycosides are usually administered by intravenous injection. They have a narrow therapeutic index, and therefore require routine monitoring of serum concentrations. The side-effects are renal- and oto-toxicity. Because of this, and the fact that they are not orally absorbed, they are generally reserved for severe infections. They are often given together with a beta-lactam antibiotic, as the combination is synergistic.

1.6.2. Glycopeptide antibiotics

The glycopeptides, such as vancomycin, inhibit bacterial cell wall synthesis, by preventing the linkages of peptidoglycan constituents. They are active against aerobic and anaerobic Gram-positive bacteria including multi-resistant staphylococci, such as Meticillin-resistant *Staphylococcus Aureus* (MRSA), although there are increasing reports of glycopeptide-resistant enterococci (GRE). Glycopeptides are usually administered as an intravenous injection. As with the aminoglycosides they may cause nephrotoxicity and ototoxicity.

1.6.3. Beta-lactam antibiotics

Beta-lactam antibiotics include penicillins (e.g. amoxicillin, flucloxacillin), cephalosporins (e.g. ceftazidime) and carbapenems (e.g. meropenem). They act by interfering with bacterial cell wall synthesis. The spectrum of activity varies hugely between the different antibacterials in this group; some are taken orally as a first line treatment of community-acquired infections, some have a narrow spectrum and are reserved for treatment of specific organisms. Others are very broad spectrum and are reserved for the treatment of life-threatening infections (by intravenous injection). Beta-lactams have a wide therapeutic index. Their main risk is administration to people with penicillin allergy, which can result in life-threatening anaphylactic reactions.
1.6.4. Quinolone antibiotics

Quinolones inhibit the replication of bacterial DNA, by blocking the activity of bacterial DNA gyrase and DNA topoisomerase, the enzymes that form DNA supercoils. Older quinolones, such as ciprofloxacin, are generally used to treat Gram-negative infections, and are the only orally available antibacterials in the UK effective against *P. aeruginosa*. The newer quinolones, such as levofloxacin, have better Gram-positive activity, but are generally not effective against MRSA. Quinolones are generally well tolerated, although may rarely cause severe tendon damage, and should be used with caution in patients with epilepsy. Most quinolones may be given both orally and intravenously.

1.6.5. Other antibiotics

Linezolid is the first of a group of antibiotics called the oxazolidinones. It works by selectively inhibiting bacterial protein synthesis, and is generally reserved for the treatment of MRSA and Glycopeptide-resistant *Enterococcus* (GRE). It may be given orally or by intravenous injection.

Colistin is a polymyxin antibiotic, one of the earliest groups of antibiotics to be discovered. It has a detergent-like action, interfering with the structure and function of the cell membrane. It is reported to have toxic side-effects including renal- and neurotoxicity, and is generally reserved for the treatment of multi-resistant Gram-negative organisms, such as *A. baumanii*, *P. aeruginosa* and *K. pneumoniae*. It is not available orally, and is administered either intravenously, or as a nebulised solution.

Since the commencement of this study a new antimicrobial, daptomycin, has been brought into clinical use. It is a novel lipopeptide antibiotic with activity against Gram positive bacteria, particularly MRSA (LaPlante and Rybak 2004).
1.7. Pharmacokinetics

Pharmacokinetics, in simple terms, is the study of what the body does to a drug. More precisely, it provides a mathematical basis to assess the time course of drugs and their effects on the body, enabling absorption, distribution, metabolism and excretion (ADME – See Figure 1.4) of drugs to be quantified. In clinical practice it is used mainly for dose adjustments of drugs with narrow therapeutic indexes, i.e. when there is little difference between toxic and therapeutic doses, particularly when there is no immediate response to the administration of a dose.
Intravascular administration

- Intravenous bolus or infusion
- Intra-arterial

Extravascular administration

- Tablets
- Sublingual
- Buccal
- Rectal
- Inhalational
- Transdermal
- Intramuscular
- Sub-cutaneous

Absorption → Distribution → Tissues and / or organs → Blood → Metabolism

Liver → Kidneys → Excretion

Bile

**Figure 1.4** Absorption, distribution, metabolism and excretion (ADME)

Figure 1.4 is a simplification of the main processes involved in ADME. For example, drugs may be excreted through other pathways, such as the burn wound.

For systemically acting drugs, other than for intravenous or intra-arterial injection (intra-vascular routes), all routes of administration require drugs to be absorbed to the site of measurement, which is usually the blood. These extravascular routes include oral, sublingual, buccal, rectal, inhalational, transdermal, intramuscular and sub-cutaneous. Therefore whilst it is assumed that all of an administered intravenous drug reaches the intravascular compartment, this may not be the case with the extravascular routes.
Additionally, it is assumed that if a drug is administered as an intravenous bolus (i.e. all the dose at once, not given over a longer period), the maximum concentration in the blood will be reached almost immediately. With the extravascular routes, absorption may take some time and therefore the maximum concentration will not be seen immediately (Figure 1.5).

![Figure 1.5. A typical plot of serum concentration versus time following the administration of a drug](image)

In figure 1.5 Drug A is administered as an intravenous bolus where the maximum serum concentration is high and occurs almost immediately. Drug B is a typical example of an oral drug where the absorption process takes place resulting in a delay before a maximum serum concentration is reached. This peak value will be lower than the peak seen for drug A for the same dose, because by the time the peak is reached, some of the drug will already have been eliminated, and also the drug may not have been completely absorbed.

Following absorption of a drug, distribution takes place, which is the reversible movement of the drug from the site of measurement (usually the blood) and usually to other organs and tissues. The rate and extent to which this takes
place is dependent on three factors; i) how well the tissues and / or organs are perfused with blood, ii) the ability of the drug to bind to plasma proteins in the blood and to tissue components, and iii) the permeability of the tissue membranes to the blood molecules (Jambhekar and Breen 2009). Because of these differences, most drugs are not distributed equally in all parts of the body. When a drug is given intravenously it may be seen that there is an initial high maximum serum concentration which drops very quickly initially. During this time the drug is in its distribution phase. Once this is complete, usually a less rapid reduction in serum concentration takes place, which is known as the elimination phase. This is demonstrated for drug A in Figure 1.6 which has the same values as in 1.5 but is shown as a logarithmic scale for serum concentration.

![Figure 1.6. A typical logarithmic plot of serum concentration versus time following administration of an intravenous drug](image)

In Figure 1.6 for the first two hours, a steeper decline in serum concentrations can be observed as the drug is undergoing distribution. (Drugs are quickly distributed to highly perfused organs like the liver, heart and kidney, but less so to less perfused tissues such as muscle and fat.) Drug A therefore has a distribution phase of approximately 2 hours. After 2 hours distribution has reached its equilibrium and the elimination phase commences.
Drugs are then eliminated from the body (i.e. removal of the active drug) by metabolism and/or excretion. Metabolism is the process of converting a drug to another molecule, which commonly occurs in the liver. Metabolites are often inactive, but some may have a pharmacological effect. (Some drugs, known as prodrugs, are inactive and need to be metabolised to another form to become active.) Drugs and metabolites are then removed from the body by the process of excretion. The primary site for this is the kidney, where a drug is lost through the urine. However, excretion may also occur in other places such as through the bile (and therefore in the faeces), also in the lungs (e.g. evaporation of alcohol) or in the breast milk of a lactating mother. Of particular significance in patients with burns is the possible excretion through the burn wound.

Whilst there are many terms relating to pharmacokinetics, there are perhaps two theoretical values that are the most important; the volume of distribution of a drug and the clearance of a drug. The volume of distribution (Vd) is a measure of how much of the drug leaves the intravascular fluid to be taken up in the organs and tissues. It is usually expressed in either litres, or litres/kg of bodyweight. The larger the Vd, the more a drug is taken up into the tissues. Clearance (Cl), usually refers to total clearance, and is the theoretical volume of blood that is completely cleared of a drug over a given time period (usually expressed in L/hr or ml/min). It is therefore not affected by the concentration of the drug.

Half-life is another common term and usually refers to the elimination half-life. This is inversely proportional to the elimination rate constant (k) (Eq. 1.1), and is the time required for the plasma concentration to decrease by one-half.

\[
k = \frac{Cl}{Vd} \quad \text{(Eq. 1.1)}
\]

K = elimination rate constant (hr\(^{-1}\)), Cl = Clearance (usually L/hr) and Vd = the volume of distribution (usually L)

Whilst the loss of fluid and proteins from the intravascular space during the acute phase of a burn may affect pharmacokinetics, in practice this is of little
clinical significance to drug dosing. This is because it lasts for a relatively short period, and the majority of drugs administered at this stage – fluids, analgesia and sedation - are titrated directly to patient response. Antibiotic therapy is unlikely to be needed during this time as infection usually develops later post-burn.

It is during the hypermetabolic phase that consideration of the impact of the pathophysiological changes on pharmacokinetics becomes important. This is particularly the case with drugs where doses cannot be quickly titrated to the patient response, such as antibiotics, anticoagulants and pre-existing medication such as antiepileptics.

1.7.1. **Absorption of drugs in patients with major burns**

The majority of drugs administered to patients with severe burns are given intravenously. This is because absorption from the gut may be abnormally affected. Intestinal permeability may be increased, so potentially increasing bioavailability (the proportion of drug absorbed). However, gastro-intestinal motility is frequently impaired in critically ill patients (Dive et al. 1994), and consequently, delayed absorption of enterally administered medicines is more likely to be of clinical significance (MacLaren et al. 2000).

1.7.2. **Protein binding of drugs in patients with major burns**

The changes in the binding of drugs to plasma proteins that occurs when a large burn is sustained may alter the distribution (see Section 1.7.3), clearance (see Section 1.7.4) and the pharmacological effect of drugs that are highly protein-bound.

The decrease in albumin concentration in the blood means that there is greater unbound fraction of drugs which normally bind to this protein, such as diazepam and phenytoin. As it is the free-fraction of the drug that is pharmacologically active, standard doses of these drugs may result in toxic effects.
Conversely, there is an increase in the production of \( \alpha_1 \)-acid glycoprotein in patients with major burns. This may result in a lower free-fraction of drugs that bind to it, such as lidocaine, pethidine and propranolol, causing standard doses to be sub-therapeutic.

### 1.7.3. Distribution of drugs in patients with major burns

Because of the changes in extra-cellular fluid volumes and in protein-binding, the volume of distribution of many drugs are increased in burns patients.

Provided that all of a drug is not retained in the intra-vascular space, the additional extra-cellular fluid may effectively dilute the drug, so reducing its concentration for a given dose. The change in extra-vascular fluid is therefore most likely to be of significance where the volume of distribution in non-burned patients is small (<30L), i.e. most of it remains in the intravascular compartment. With larger volumes of distribution, only a small fraction of the drug is present in the intravascular compartment. An increase in the extra-cellular fluid volume would therefore lead to only minor changes in the volume of distribution and so only to minor differences in plasma concentration of these drugs.

Drugs that are highly protein-bound will be retained in the intra-vascular space, and will generally have a small volume of distribution. A decrease in the number of protein molecules – as in the case of albumin - available for the drug to bind may therefore increase the volume of distribution. For drugs that bind to \( \alpha_1 \)-acid glycoprotein, where levels increase in burns, there may be a decrease in the volume of distribution.

### 1.7.4. Clearance of drugs in patients with major burns

There are three main factors that are altered in severe burns that may affect clearance: protein binding, the presence of additional elimination pathways and hypermetabolism.
1.7.4.1. The effect of protein binding on clearance

The impact of the change in protein binding that occurs in severe burns differs between drugs with high extraction ratios and those with low extraction ratios. The extraction ratio is the ratio of the rate of elimination of a drug from an organ to the rate at which the drug enters it. Therefore a drug with a high extraction ratio means that a large proportion of the drug is removed. The term is usually applied to the liver, although can be used for other organs such as the kidney.

For high extraction ratio drugs, such as morphine, total clearance is mainly dependent on blood flow. The effect of plasma protein concentrations is minimal as the liver is able to separate the drug from the protein and then metabolise it (Dhillon and Kostrzewski 2006). Therefore the effect of plasma protein concentrations on clearance is minimal.

For low extraction ratio drugs, such as phenytoin, only a small proportion of drug is usually removed, so the effect of changes in blood flow is minimal. Instead, factors that affect the ability of the organ to remove the drug from the blood are more important. In patients with severe burns, hepatic enzyme activity may be impaired (Ciaccio and Fruncillo 1979), metabolism slowed and clearance reduced. Conversely, with low extraction ratio drugs, the forces that hold the drug molecule to the protein molecule are stronger than the ability of the liver to pull it away (Dhillon and Kostrzewski 2006). Therefore if there is a reduction in the number of proteins available to bind to, more free drug is available to be removed and total clearance may increase.

1.7.4.2. The effect of additional elimination pathways on clearance

The presence of a large burn may mean that clearance is increased, due to the loss of drug through the burn wound (Glew, Moellering and Burke 1976).

1.7.4.3. The effect of hypermetabolism on clearance

The increase in cardiac output will increase blood flow though the kidneys and liver, which may result in increased renal clearance of drugs. The increase in
hepatic blood flow in burns patients should result in a greater hepatic clearance of high-extraction drugs. As discussed in Section 1.7.4.1, the effect of changes in blood flow is minimal on the clearance of low extraction drugs.

### 1.7.5. Elimination half-life of drugs in patients with major burns

As elimination half-life is dependent on both the volume of distribution and clearance, it may, in the case of patients with burns, be shorter or longer than normal. A greater clearance should shorten the half-life. A larger volume of distribution would be expected to lengthen the half-life, due to the interstitial fluid acting as a reservoir from which the drug slowly returns to the circulation.

### 1.8. Pharmacokinetic studies of antibiotics in patients with burns

The majority of pharmacokinetic studies in burns patients have been with antibiotics. This is likely to be because:

- infection is a major cause of mortality in severely burned patients
- outcome may be improved by early achievement of effective peak antibiotic concentrations, particularly if achieved within the first 72 hours after the onset of sepsis (Glew, Moellering and Burke 1976; Zaske et al. 1981; Moore, Smith and Lietman 1984)
- the dose cannot be titrated to response

Whilst there have been pharmacokinetic studies in drugs other than antibiotics (Jaehde and Sorgel 1995), as the subject of this thesis relates to antibiotics, this section will discuss pharmacokinetic studies in this group of drugs only.

The first published studies of pharmacokinetics in patients with burns were of gentamicin (Glew, Moellering and Burke 1976; Sawchuk and Zaske 1976; Zaske et al. 1976). This was probably because serum gentamicin concentrations were measured as part of routine clinical practice in all patients with the dose being adjusted to achieve appropriate peak and trough levels. Such data allowed the calculation of pharmacokinetic parameters. As with many studies in burns, patient numbers were relatively small, a reflection of the
relatively low numbers of patients with major burns. Also because of the low numbers, there are many unmatched variables that may affect pharmacokinetics such as age, weight, size of burn, time since the burn and renal function. Weight is particularly difficult to measure, as it may vary hugely almost on a day-to-day basis, not only because of the extent of the oedema, but also the exudate in the burns dressings, which when replaced with fresh dressings may make the patient’s recorded weight significantly less.

Despite these limitations, pharmacokinetic studies in burns patients are valuable, and should be applied to clinical practice whenever possible.

1.8.1. Pharmacokinetic studies of aminoglycosides in patients with burns

Pharmacokinetic studies show that the clearance of aminoglycosides is significantly increased and the half-life significantly decreased compared with values published for non-burn patients. Most studies show no difference in the volume of distribution, compared with healthy people (approximately 0.25L/kg) except for Zaske et al (1976) which showed an increase in the five children studied. In practice, this has meant increased dose requirements for burns patients (Zaske et al. 1976; Zaske, Sawchuk and Strate 1978; Kopcha, Fant and Warden 1991). Later, Zaske et al (1991) proposed a dosing schedule (Table 1.6) based on their findings that therapeutic doses were dependent on age and renal function: patients under the age of 30 years, without renal impairment, require higher doses than the 3-5mg/kg/day which would usually be the case for non-burn patients.
Table 1.6. Proposed dosing schedule for gentamicin in major burns patients without renal impairment. Adapted from Zaske et al (1991).

The recommended total daily dose of gentamicin decreases with age in patients with major burns (assuming no renal impairment).

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose (mg/kg)</th>
<th>Dosing interval</th>
<th>Total daily dose (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 10</td>
<td>1.7</td>
<td>Every 4 hours</td>
<td>10.0</td>
</tr>
<tr>
<td>11 – 30</td>
<td>1.9</td>
<td>Every 6 hours</td>
<td>7.5</td>
</tr>
<tr>
<td>31 – 60</td>
<td>1.7</td>
<td>Every 8 hours</td>
<td>5.0</td>
</tr>
<tr>
<td>over 60</td>
<td>1.5</td>
<td>Every 12 hours</td>
<td>3.0</td>
</tr>
</tbody>
</table>

The doses proposed were suggested starting doses, with the dose and/or frequency being adjusted according to peak and trough serum concentrations. Doses as high as 17.8mg/kg/day have been reported to be necessary for burns patients to achieve therapeutic serum concentrations (Hollingsed et al. 1993).

In recent years, the administration of aminoglycosides in many non-burn populations has moved from being given two or three times a day, to once daily (Gilbert 1991). This is because it is thought to be less toxic and at least equally effective (Barza et al. 1996). It also reduces nursing time, and is simpler to monitor. In burns there was concern that the shorter half life could mean that the post-antibiotic effect⁴ may not last for the 24 hour period. This was investigated by Hoey et al (1997), who used pharmacokinetic data from patients receiving gentamicin or tobramycin to calculate pharmacokinetic parameters for simulated single doses of 5 to 7 mg/kg. As with other studies, they found that there was a wide variation in the pharmacokinetic parameters, with some patients with extrapolated concentrations falling below 0.1mg/L (effectively aminoglycoside-free) as early as 7.5 and 8 hours for 5mg/kg and 7mg/kg doses respectively, whereas other patients did not have concentrations below 0.1mg/L

---

⁴ Post-antibiotic effect (PAE) is the persistent suppression of bacterial growth following exposure to an antimicrobial i.e. the time it takes for an organism to recover from the effects of exposure to an antimicrobial. In practice this means that the antibiotic is still effective for some time after serum concentrations are effectively drug-free.
for the whole 24 hour period with either dose regimen. This was despite the exclusion of patients with renal impairment (an estimated creatinine clearance below 60ml/min). The length of the post antibiotic effect (PAE) of the aminoglycosides is dependent on several factors, including the type of infecting organism and also the peak antibiotic serum concentration, and can range from 0.5 to 7.5 hours (Lacy et al. 1998). With 15% of their patients in the study by Hoey et al. (1997) simulated to have levels below 0.1mg/L for more than twelve hours, it is possible that there would have been treatment failure. For those patients whose serum levels did not drop to below 0.1mg/L for the whole 24-hour period, there was increased risk of toxicity and the development of resistance by the infecting organism (Daikos, Lolans and Jackson 1991; Tulkens 1991). The authors concluded that severely burned patients may not be candidates for once-daily administration of aminoglycosides. The use of extended dose administration of aminoglycosides is discussed in more detail in Chapter 7.

Studies of other aminoglycosides such as amikacin and tobramycin have been consistent with the findings of the gentamicin studies, with wide inter-patient variations in pharmacokinetic parameters, and in general the need for larger doses compared with those recommended for non-burn patients (Zaske, Sawchuk and Strate 1978; Kopcha, Fant and Warden 1991).

Pharmacokinetic studies of aminoglycosides up until the start of this thesis in 2002 are summarised in Table 1.7. Since then there have been four further studies of note of the pharmacokinetics of aminoglycosides in patients with burns (Conil et al. 2006; Bracco et al. 2008; Kim, Lah and Yim 2008; Caetano et al. 2009). In a study of adult burn patients receiving high-dose once-daily amikacin (20mg/kg, compared with the usual maximum of 15mg/kg in the UK), only 18 of the 38 patients achieved the target peak concentration (Conil et al. 2006). This was set as six to eight times the breakpoint (48 to 64mg/L), which is higher than the once-daily peak used in other papers (Marik et al. 1991). Whilst both the mean amikacin Vd and Cl were higher than values published for healthy subjects, statistical significance was not measured. Mean amikacin clearance was higher in patients who had creatinine clearances of more than
120ml/min compared with the mean value for patients with creatinine clearances of less than this value (p<0.009). The mean elimination half-life was similar to those quoted for healthy volunteers. The authors suggested an initial dose of 25mg/kg to 30mg/kg in patients with TBSA burn > 15% and / or those with creatinine clearances of more than 120ml/min. In their conference poster Caetano et al (2009) also concluded that the standard dose of amikacin was insufficient for some patients with major burns.

Bracco et al (2008) studied the pharmacokinetics of once-daily tobramycin, and found no increase in clearance in patients with burns. Whilst it was concluded that the drug had both an increased volume of distribution and half-life in patients with burns, there was wide interpatient variation. Kim et al (2008) did find an increase in the clearance of arbekacin (given twice-daily), an aminoglycoside not used in the UK, compared with values reported for patients without burns. They also noted that the volume of distribution increased proportionally with Burn Index (BI). The calculation of the Burn Index was not explained or referenced. The authors concluded that higher doses may be required in patients with burns, especially those with a BI over 20.
<table>
<thead>
<tr>
<th>Patients</th>
<th>TBSA (%)</th>
<th>TPB (d)</th>
<th>Dosage regimen</th>
<th>$C_{\text{max}}$ (mg/L)</th>
<th>$C_{\text{trough}}$ (mg/L)</th>
<th>$t^{1/2}$ (h)</th>
<th>Vd (L/kg)</th>
<th>Cl (ml/min)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gentamicin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 Ch</td>
<td>30 - 92</td>
<td>NA</td>
<td>0.9 – 2 mg/kg</td>
<td>2.9&lt;sup&gt;c&lt;/sup&gt;</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.1 – 3 mg/kg</td>
<td>4.1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>5 Ch</td>
<td>58.0 ± 25.4</td>
<td>21.8 ± 13.3</td>
<td>12.8 ± 7.4 mg/kg/d</td>
<td>7.6 ± 3.4</td>
<td>NA</td>
<td>1.1 ± 0.44</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>9 Ad</td>
<td>54.4 ± 16.6</td>
<td>19.4 ± 16.8</td>
<td>7.25 ± 1.8 mg/kg/d</td>
<td>7.7 ± 2.9</td>
<td>NA</td>
<td>3.3 ± 1.1</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>8 Ad</td>
<td>NA</td>
<td>4.8 ± 2.3</td>
<td>14.3 ± 2.1 mg/kg/d</td>
<td>7.8 ± 3.3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2.8 ± 2.3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2.5 ± 1.4&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.26 ± 0.01&lt;sup&gt;c&lt;/sup&gt;</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>3 Ch</td>
<td>NA</td>
<td>4.8 ± 2.3</td>
<td>7.21 ± 1.4 mg/kg/d</td>
<td>9.7 ± 1.1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2.1 ± 1.0&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.2 ± 0.5&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.2 ± 0.02&lt;sup&gt;c&lt;/sup&gt;</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>66 Ad</td>
<td>12 - 90</td>
<td>NA</td>
<td>9.2 ± 3.6 mg/kg/d</td>
<td>7.6 ± 0.9&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.4 ± 0.8&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2.06 ± 1.85&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.22 (0.11-0.52)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>6 Ch</td>
<td>28.1 ± 4.0</td>
<td>20.8 ± 10.0</td>
<td>13.7 ± 1.5 mg/kg/d</td>
<td>NA</td>
<td>2.08 ± 0.17&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.53 ± 0.07</td>
<td>NA</td>
<td></td>
<td>Hollingsed et al (1993)</td>
</tr>
<tr>
<td>Gentamicin and Tobramycin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 Ad</td>
<td>48.4 ± 21.4</td>
<td>9.3 ± 6.6</td>
<td>5.1 mg/kg</td>
<td>7.7 ± 2.1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.5 ± 1.1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2.7 ± 1&lt;sup&gt;c,f&lt;/sup&gt;</td>
<td>0.26 ± 0.09&lt;sup&gt;c,f&lt;/sup&gt;</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>52 Ad</td>
<td>37 (1-80)</td>
<td>11.8 (1-84)</td>
<td>5 mg/kg/d</td>
<td>15.4 (6.4 – 33.7)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.03 (0-0.3)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2.2 (1.0-3.9)</td>
<td>0.27 (0.2 – 0.5)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>7 mg/kg/d</td>
<td>21.6 (9.0-47.2)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.04 (0-0.4)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2.2 (1.0-3.9)</td>
<td>0.27 (0.2 – 0.5)</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

Table 1.7. Pharmacokinetic studies of aminoglycosides in patients with burns up until 2002. Adapted from Blanchet et al (2008)<sup>a</sup>

<sup>a</sup> Values are expressed as mean ± SD or range; <sup>b</sup> Single dose; <sup>c</sup> Steady state; <sup>d</sup> Exudation phase; <sup>e</sup> Repaired phase; <sup>f</sup> in Litres, not L/kg; <sup>g</sup> gentamicin and tobramycin have same dosage and pharmacokinetics

<sup>Ad</sup> = adults; <sup>Ch</sup> = children; <sup>Cl</sup> = total body clearance; <sup>C_{max}</sup> = maximum plasma concentration; <sup>C_{trough}</sup> = trough plasma concentration; <sup>NA</sup> = no data available; <sup>t^{1/2}</sup> = elimination half-life; <sup>TBSA</sup> = total burn surface area; <sup>TPB</sup> = time post-burn; <sup>Vd</sup> = volume of distribution
<table>
<thead>
<tr>
<th>Patients</th>
<th>TBSA (%)</th>
<th>TPB (d)</th>
<th>Dosage regimen</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (mg/L)</th>
<th>C&lt;sub&gt;trough&lt;/sub&gt; (mg/L)</th>
<th>t½ (h)</th>
<th>Vd (L/kg)</th>
<th>Cl (ml/min)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobramycin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 Ad</td>
<td>33 ± 21.3</td>
<td>4 - 35</td>
<td>1.42 ± 0.22</td>
<td>7.5 ± 1.3</td>
<td>NA</td>
<td>0.85 ± 0.19</td>
<td>28.3 ± 7.7&lt;sup&gt;f&lt;/sup&gt;</td>
<td>NA</td>
<td>Loirat &lt;i&gt;et al&lt;/i&gt; (1978)</td>
</tr>
<tr>
<td>Amikacin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 Ad</td>
<td>41.8 ± 19.8</td>
<td>11.5 ± 9.6</td>
<td>30.9 ± 2.9 mg/kg/d</td>
<td>29.2 ± 9.9&lt;sup&gt;b&lt;/sup&gt;</td>
<td>NA</td>
<td>1.4 ± 0.54&lt;sup&gt;b&lt;/sup&gt;</td>
<td>NA</td>
<td>NA</td>
<td>Zaske &lt;i&gt;et al&lt;/i&gt; (1978)</td>
</tr>
<tr>
<td></td>
<td>36.6 ± 12.5</td>
<td>NA</td>
<td>8.82 ± 2.3 mg/kg</td>
<td>20.6 ± 7.5&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>5.4 ± 4.8&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Palayret &lt;i&gt;et al&lt;/i&gt; (1979)</td>
</tr>
<tr>
<td>6 Ad</td>
<td>31 ± 5.5</td>
<td>3-4</td>
<td>7.5 mg/kg</td>
<td>14.1 ± 3.9&lt;sup&gt;b,d&lt;/sup&gt;</td>
<td>NA</td>
<td>2.63 ± 0.48&lt;sup&gt;b,d&lt;/sup&gt;</td>
<td>0.5 ± 0.12&lt;sup&gt;b,d&lt;/sup&gt;</td>
<td>152.1 ± 24.3&lt;sup&gt;b,d&lt;/sup&gt;</td>
<td>Vincon &lt;i&gt;et al&lt;/i&gt; (1986)</td>
</tr>
<tr>
<td></td>
<td>&gt;15</td>
<td></td>
<td>7.5 mg/kg</td>
<td>18.5 ± 2.4&lt;sup&gt;b,e&lt;/sup&gt;</td>
<td>NA</td>
<td>2.62 ± 0.22&lt;sup&gt;b,e&lt;/sup&gt;</td>
<td>0.42 ± 0.06&lt;sup&gt;b,e&lt;/sup&gt;</td>
<td>109.2 ± 13.7&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>38 Ch</td>
<td>52.5 ± 15.5</td>
<td>NA</td>
<td>40-60 mg/kg/day</td>
<td>NA</td>
<td>NA</td>
<td>1.3 ± 0.3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.39 ± 0.1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>58.3 ± 21.7&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Kopcha &lt;i&gt;et al&lt;/i&gt; (1991)</td>
</tr>
</tbody>
</table>

Table 1.7 continued. Pharmacokinetic studies of aminoglycosides in patients with burns up until 2002. Adapted from Blanchet <i>et al</i> (2008)<sup>a</sup>

<sup>a</sup> Values are expressed as mean ± SD or range; b Single dose; c Steady state; d Exudation phase; e Repaired phase; f in Litres, not L/kg; g gentamicin and tobramycin have same dosage and pharmacokinetics

Ad = adults; Ch = children; Cl = total body clearance; C<sub>max</sub> = maximum plasma concentration; C<sub>trough</sub> = trough plasma concentration; NA = no data available; t½ = elimination half-life; TBSA = total burn surface area; TPB = time post-burn; Vd = volume of distribution
1.8.2. **Pharmacokinetic studies of glycopeptides in patients with burns**

The glycopeptides used in clinical practice are vancomycin and teicoplanin. Vancomycin, as with the aminoglycosides, is monitored by measuring serum concentrations and therefore it is not surprising that this was the next antibiotic to be the subject of pharmacokinetic studies. The first study (Rotschafer, Crossley and Zaske 1982) showed no difference in the pharmacokinetics compared with those without burns when given as an intermittent infusion. Other studies have also found no difference in the volume of distribution (Garrelts and Peterie 1988; Rybak et al. 1990), but one (Garrelts and Peterie 1988) has reported a shorter half-life, with a 78% increase in the dose required to achieve similar trough levels as for non-burn patients. Further work (Conil et al. 1994) was undertaken when continuous infusion of vancomycin was introduced. The rational for this method of administration was that vancomycin is a time-dependent antibiotic, with maximum effectiveness thought to be at four times above the minimum inhibitory concentration\(^5\) (Weinbren 1999). Conil et al. (1994) found that at the dose usually recommended for patients without burns (35mg/kg/day) only those who were over the age of 58 achieved therapeutic levels of > 15mg/L. The other patients required a dose of 40mg/kg/day.

Pharmacokinetic studies of glycopeptides up to the commencement of the thesis (2002) are summarised in Table 1.8. More recently Dailly et al. (2008) found a significant relationship between vancomycin clearance and creatinine clearance. They proposed a formula for calculating the initial dose of continuous infusion vancomycin, with the only variables being creatinine clearance and target vancomycin concentration. The authors acknowledge that the formula does not take into account all of the factors that may affect vancomycin dosing.

Dolton et al. (2010) compared the pharmacokinetics of vancomycin in patients with burns with non-burned subjects. As with other studies, they found no difference between the groups in the volume of distribution, but those with burns

\(^5\) The minimum inhibitory concentration (MIC) is the lowest concentration of the antibiotic that results in inhibition of visible growth (i.e. colonies on a plate or turbidity in broth culture) under standard conditions.
had a significantly (p<0.001) higher clearance (5.9 ± 3.1L/h, n = 37) than those without (3.4 ± 1.8L/hr, n = 33). As a result the burned patients, receiving a dose of 1g twelve-hourly, had significantly lower serum trough concentrations (median 6.4mg/L, range 0.2 to 22.3). The use of vancomycin in severely burned patients is discussed further in Chapter 8.

In non-burn patients, it is generally not thought to be necessary to measure serum concentrations of the glycopeptide teicoplanin. However the manufacturers advise that the determination of serum concentrations may optimise therapy (ABPI 2001). This recommendation is supported for patients with burns by the work of Steer et al (1996). Following administration of a single dose of teicoplanin the clearance was significantly greater in the five children in their study (per kg bodyweight) compared with the fifteen adults. There was considerable variation in the pharmacokinetic parameters, but no correlation could be found between serum concentrations at 12 and 24 hours, and age, burn surface area or serum creatinine concentration in adults. They did find a significant negative correlation between serum total protein concentration and serum teicoplanin concentrations. (The data from the children did not undergo regression analysis due to the small numbers.) Of note is that the teicoplanin was administered either within 48 hours of admission or immediately prior to excision and grafting. Those who received their dose in the first 48 hours, may not have reached the hypermetabolic phase, when antibiotics are usually administered. Therefore it may be expected that even higher doses of teicoplanin are required when used in clinical practice.
<table>
<thead>
<tr>
<th>Patients</th>
<th>TBSA (%)</th>
<th>TPB (d)</th>
<th>Dosage regimen</th>
<th>$C_{\text{max}}$ (mg/L)</th>
<th>$C_{\text{trough}}$ (mg/L)</th>
<th>$t_{1/2}$ (h)</th>
<th>Vd (L/kg)</th>
<th>Cl (ml/min)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21 Ad</td>
<td>NA</td>
<td>250 or 500mg</td>
<td>NA</td>
<td>NA</td>
<td>$6.1 \pm 2.5^b$</td>
<td>$0.62 \pm 0.44^b$</td>
<td>77.1 ± 33.4$^b$</td>
<td>Rotschafer et al (1982)</td>
<td></td>
</tr>
<tr>
<td>9 Ad</td>
<td>$24.0 \pm 14.1$</td>
<td>$34.3 \pm 33.6$</td>
<td>$46.6 \pm 20$mg/kg</td>
<td>$27.0 \pm 2.6^c$</td>
<td>$8.1 \pm 3.0^c$</td>
<td>$3.84 \pm 1.02^c$</td>
<td>$0.51 \pm 0.09^c$</td>
<td>$97.0 \pm 27.8^c$</td>
<td>Garrels et al (1988)</td>
</tr>
<tr>
<td>10 Ad</td>
<td>$50 \pm 3.0$</td>
<td>500mg 6h or 8h</td>
<td>NA</td>
<td>NA</td>
<td>$15.0 \pm 13.0^c$</td>
<td>NA</td>
<td>NA</td>
<td>93.9 ± 56.4$^c$</td>
<td>Brater et al (1986)</td>
</tr>
<tr>
<td>10 Ad</td>
<td>$30.9 \pm 14.9$</td>
<td>$18.3 \pm 42.7 \pm \text{NA}$</td>
<td>NA</td>
<td>$18.3 \pm 11.7 \pm 18.5$mg/kg</td>
<td>NA</td>
<td>$0.59 \pm 0.17^c$</td>
<td>142.8 ± 34.5$^c$</td>
<td>Rybak et al (1990)</td>
<td></td>
</tr>
<tr>
<td>10 Ad</td>
<td>$28.8 \pm 16.2$</td>
<td>$31.3 \pm 750 \pm \text{NA}$</td>
<td>$48.6 \pm 235$mg/day</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Zokula et al (1989)</td>
<td></td>
</tr>
<tr>
<td>Teicoplanin</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>8 Ad</td>
<td>UBS &gt; 90</td>
<td>NA</td>
<td>10–14mg/kg/day</td>
<td>$25.9 \pm 4.5^c,g$</td>
<td>$7.5 \pm 1.8^c,g$</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Rio et al (1987)</td>
</tr>
<tr>
<td>12 Ad</td>
<td>UBS &lt; 90</td>
<td>NA</td>
<td>5–9mg/kg/day</td>
<td>$27.5 \pm 3.3$</td>
<td>$7.4 \pm 1.3^c,g$</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>10 Ad</td>
<td>$61.6 \pm 19.6$</td>
<td>$2-3$</td>
<td>$10$mg/kg</td>
<td>$136 \pm 58.4^b,d$</td>
<td>$7.9 \pm 2.6^b,d$</td>
<td>$64.3 \pm 53.3^b,d$</td>
<td>$0.9 \pm 0.37^b,d$</td>
<td>$0.34 \pm 0.1^b,d$</td>
<td>Potel et al (1990)</td>
</tr>
<tr>
<td>10 Ad</td>
<td>$27.6 \pm 2.5$</td>
<td>$2-3$</td>
<td>$10$mg/kg</td>
<td>$88.5 \pm 38^b,d$</td>
<td>$6.6 \pm 1.9^b,d$</td>
<td>$38.9 \pm 12.9^b,d$</td>
<td>$0.86 \pm 0.39^b,d$</td>
<td>$0.29 \pm 0.14^b,d,e$</td>
<td></td>
</tr>
</tbody>
</table>

See overleaf for footnotes

*Table 1.8. Pharmacokinetic studies of glycopeptides in patients with burns up to 2002. Adapted from Blanchet et al (2008)*

68
<table>
<thead>
<tr>
<th>Patients</th>
<th>TBSA (%)</th>
<th>TPB (d)</th>
<th>Dosage regimen</th>
<th>Cmax (mg/L)</th>
<th>Ctrough (mg/L)</th>
<th>t½ (h)</th>
<th>Vd (L/kg)</th>
<th>Cl (ml/min)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teicoplanin continued</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 Ad</td>
<td>30 (15 - 60)</td>
<td>2</td>
<td>12mg/kg</td>
<td>NA</td>
<td>8.3</td>
<td>26 ((4.6 - 12.9)^b)</td>
<td>0.45 ((0.20 - 0.52))</td>
<td>0.25 ((0.18 - 30)^{b,h,i})</td>
<td>Steer et al (1996)</td>
</tr>
<tr>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 Ch</td>
<td>15 (10 – 30)</td>
<td>2</td>
<td>12mg/kg</td>
<td>NA</td>
<td>5.2</td>
<td>38 ((4.2 - 6.0)^b)</td>
<td>0.69 ((0.62 - 0.82))</td>
<td>0.3 ((0.23 - 0.48)^{b,h,i})</td>
<td></td>
</tr>
<tr>
<td></td>
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<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Ad</td>
<td>60</td>
<td>10</td>
<td>1200mg/day</td>
<td>69.9^c</td>
<td>4.8^c</td>
<td>9.26^c</td>
<td>0.77^c</td>
<td>64.2^c</td>
<td>Lesne-Hulin et al (1997)</td>
</tr>
</tbody>
</table>

Table 1.8 continued. Pharmacokinetic studies of glycopeptides in burns patients up to 2002. Adapted from Blanchet et al (2008)^a

a Values are expressed as mean ± SD or range; b Single dose; c Steady state; d Pharmacokinetic parameters estimated with three-compartment model; e Values expressed as mcg/g; f Values expressed as ml/min/kg; g values expressed as mean ± standard error of mean; h values expressed as median (range); i Pharmacokinetic parameters estimated with two-compartment model; Eschar.

Ad = adults; Ch = children; Cl = total body clearance; Cmax = maximum plasma concentration; Ctrough = trough plasma concentration; NA = no data available; t½ = elimination half-life; TBSA = total burn surface area; TPB = time post-burn; UBS = unit burn standard; Vd = volume of distribution.
1.8.3. Pharmacokinetic studies of beta-lactam antibiotics in patients with burns

Pharmacokinetic studies of beta-lactam antibiotics undertaken before the start of this thesis (i.e. up until 2002) are summarised in Table 1.9

1.8.3.1. Pharmacokinetic studies of penicillins in patients with burns

Drugeone et al (1984) found that the pharmacokinetics of azlocillin were similar to those in healthy volunteers, although there was an increase in non-renal clearance, which would suggest that the drug is lost by routes other than through the kidney, such as through the burn wound.

By contrast, with piperacillin/tazobactam Bourget et al (1996) noted an increased volume of distribution of both components and an elimination half-life of two to three times the length of healthy volunteers. It might be expected that if the half-life is longer, clearance would be reduced. However, this is not always the case, as the increased interstitial fluid volume associated with major burns, could act as a reservoir, from which drugs slowly return to the circulation. This is the case with piperacillin which may have up to a three- to four- times increase in the clearance rate compared with healthy subjects (Shikuma et al. 1990). Because of the pharmacokinetic differences, Bourget et al (1996) suggested that the frequency of dosing of piperacillin/tazobactam should be increased from the usual eight-hourly to every six hours.

Another drug combination, ticarcillin with clavulanic acid has also been studied in burns patients. Adam et al (1989) found that the volume of distribution and half-life of both drugs were increased in burns, but particularly the clavulanic acid. The clearance was also increased and the investigators recommended that the highest dose should be used in burns patients.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Patients</th>
<th>TBSA (%)</th>
<th>TPB (d)</th>
<th>Dosage regimen</th>
<th>$C_{\text{max}}$ (mg/L)</th>
<th>$C_{\text{trough}}$ (mg/L)</th>
<th>$t^{\text{1/2}}$ (h)</th>
<th>Vd (L/kg)</th>
<th>Cl (ml/min)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azlocillin</td>
<td>5 Ad</td>
<td>22.6 ± 15.1</td>
<td>&lt;5</td>
<td>80mg/kg</td>
<td>168.6 ± 47.1</td>
<td>NA</td>
<td>1.48 ± 0.27$^b$</td>
<td>0.37 ± 0.11$^b$</td>
<td>152 ± 41.5$^{b,c}$</td>
<td>Druegon et al (1984)</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>9 Ad</td>
<td>49 ± 21</td>
<td>7 ± 1.4</td>
<td>2g/6h</td>
<td>NA</td>
<td>NA</td>
<td>3.92 ± 2.42$^b$</td>
<td>0.27 ± 0.04$^b$</td>
<td>106.7 ± 60$^b$</td>
<td>Friedrich et al (1991)</td>
</tr>
<tr>
<td>Cefepime</td>
<td>13 Ad</td>
<td>36 ± 17</td>
<td>9 ± 3</td>
<td>2g</td>
<td>110 ± 23$^b$</td>
<td>2.3 ± 1.6$^{b,e}$</td>
<td>2.8 ± 0.6$^b$</td>
<td>0.43 ± 0.1$^b$</td>
<td>146.7 ± 40$^b$</td>
<td>Bonapace et al (1999)</td>
</tr>
<tr>
<td></td>
<td>6 Ad</td>
<td>31.5 ± 23.6</td>
<td>&gt;2</td>
<td>2g/12h</td>
<td>89 - 146$^b$</td>
<td>2.1 ± 1.1$^e$</td>
<td>2.45 ± 0.56$^b$</td>
<td>0.36 ± 0.1$^b$</td>
<td>152 ± 25.2$^b$</td>
<td>Sampol et al (2000)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>71.5 - 243$^{c}$</td>
<td>2.4 ± 0.95$^d$</td>
<td>2.62 ± 0.53$^d$</td>
<td>0.35 ± 0.1$^d$</td>
<td>133 ± 29.1$^d$</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>33 ± 41.6$^{d,i,g}$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>8 Ad</td>
<td>47.7 ± 18.4</td>
<td>5.63 ± 6.23</td>
<td>1g/8h</td>
<td>64 ± 9$^b$</td>
<td>4.3 ± 2.8$^b$</td>
<td>2.7 ± 0.9$^b$</td>
<td>0.38 ± 0.1$^b$</td>
<td>139 ± 25$^b$</td>
<td>Walstad Aanderud and Thurmann-Nielsen (1988)</td>
</tr>
<tr>
<td>Imipenem</td>
<td>11 Ad</td>
<td>43.4 ± 20.2</td>
<td>11.6 ± 5.8</td>
<td>0.5g/6h</td>
<td>13.5 - 28.5$^b$</td>
<td>NA</td>
<td>1.11 ± 0.43$^a$</td>
<td>0.23 ± 0.04$^b$</td>
<td>215 ± 58$^b$</td>
<td>Boucher et al (1990)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>16.6 - 37.1$^d$</td>
<td>NA</td>
<td>1.13 ± 0.47$^d$</td>
<td>0.21 ± 0.08$^d$</td>
<td>200 ± 65$^{c,d}$</td>
<td></td>
</tr>
</tbody>
</table>

See overleaf for footnotes

*Table 1.9. Pharmacokinetic studies up to 2002 of beta-lactams in patients with burns. Adapted from Blanchet et al (2008)*
<table>
<thead>
<tr>
<th>Drug</th>
<th>Patients</th>
<th>TBSA (%)</th>
<th>TPB (d)</th>
<th>Dosage regimen</th>
<th>Cmax (mg/L)</th>
<th>Ctrough (mg/L)</th>
<th>t½ (h)</th>
<th>Vd (L/kg)</th>
<th>Cl (ml/min)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piperacillin</td>
<td>9 Ad</td>
<td>20 - 80</td>
<td>6 - 21</td>
<td>3 – 4 g/dose</td>
<td>NA</td>
<td>NA</td>
<td>3.6</td>
<td>0.7</td>
<td>247.8</td>
<td>Shikuma et al (1990)</td>
</tr>
<tr>
<td>PIPeracillin/</td>
<td>10 Ad</td>
<td>40.8 ± 3.1</td>
<td>12.4 ± 1.4</td>
<td>PIP 4g/6h</td>
<td>322.2 ± 39&lt;sup&gt;b,h&lt;/sup&gt;</td>
<td>26.3 ± 8.5&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.8 ± 0.3&lt;sup&gt;d,h&lt;/sup&gt;</td>
<td>0.30 ± 0.06&lt;sup&gt;d,h&lt;/sup&gt;</td>
<td>140.5 ± 22.8&lt;sup&gt;d,h&lt;/sup&gt;</td>
<td>Bourget et al (1996)</td>
</tr>
<tr>
<td>TAZobactam</td>
<td></td>
<td></td>
<td></td>
<td>TAZ 0.5g/6h</td>
<td>368.4 ± 40.1&lt;sup&gt;d,h&lt;/sup&gt;</td>
<td>21.0 ± 9.1&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1.5 ± 0.3&lt;sup&gt;d,h&lt;/sup&gt;</td>
<td>0.20 ± 0.03&lt;sup&gt;d,h&lt;/sup&gt;</td>
<td>123.2 ± 19.9&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TAZ 0.5g/6h</td>
<td>21.9 ± 2.3&lt;sup&gt;d,h&lt;/sup&gt;</td>
<td>1.9 ± 0.6&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1.7 ± 0.3&lt;sup&gt;d,h&lt;/sup&gt;</td>
<td>0.4 ± 0.03&lt;sup&gt;d,h&lt;/sup&gt;</td>
<td>249 ± 35.9&lt;sup&gt;d,h&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TAZ 0.5g/6h</td>
<td>18.6 ± 1.7&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1.4 ± 0.3&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1.4 ± 0.3&lt;sup&gt;d,h&lt;/sup&gt;</td>
<td>0.5 ± 0.06&lt;sup&gt;d,h&lt;/sup&gt;</td>
<td>309.5 ± 43.8&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>TICarcillin/</td>
<td>7 Ad</td>
<td>43 (22 – 58)</td>
<td></td>
<td>TIC 5g/8 or 12 h</td>
<td>488.6 ± 69.7&lt;sup&gt;d,h&lt;/sup&gt;</td>
<td>NA</td>
<td>1.6 ± 0.11&lt;sup&gt;d,h&lt;/sup&gt;</td>
<td>0.46 ± 0.04&lt;sup&gt;d,h&lt;/sup&gt;</td>
<td>389 ± 39.7&lt;sup&gt;d,h&lt;/sup&gt;</td>
<td>Adam et al (1989)</td>
</tr>
<tr>
<td>CLAvulanic Acid</td>
<td></td>
<td></td>
<td></td>
<td>CLA 0.2g/8 or 12 h</td>
<td>16.6 ± 1.8&lt;sup&gt;d,h&lt;/sup&gt;</td>
<td>NA</td>
<td>2.4 ± 0.19&lt;sup&gt;d,h&lt;/sup&gt;</td>
<td>0.46 ± 0.04&lt;sup&gt;d,h&lt;/sup&gt;</td>
<td>252 ± 14.7&lt;sup&gt;d,h&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8 Ad</td>
<td>3 (3-5)</td>
<td></td>
<td>TIC 5g/8 or 12 h</td>
<td>572.7 ± 76.5&lt;sup&gt;d,h&lt;/sup&gt;</td>
<td>NA</td>
<td>1.4 ± 0.08&lt;sup&gt;d,h&lt;/sup&gt;</td>
<td>0.44 ± 0.03&lt;sup&gt;d,h&lt;/sup&gt;</td>
<td>404 ± 25.6&lt;sup&gt;d,h&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CLA 0.2g/8 or 12 h</td>
<td>14.0 ± 1.0&lt;sup&gt;d,h&lt;/sup&gt;</td>
<td>NA</td>
<td>2.2 ± 0.15&lt;sup&gt;d,h&lt;/sup&gt;</td>
<td>0.48 ± 0.03&lt;sup&gt;d,h&lt;/sup&gt;</td>
<td>276 ± 15.8&lt;sup&gt;d,h&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

Table 1.9 continued. Pharmacokinetic studies up to 2002 of beta-lactams in patients with burns. Adapted from Blanchet et al (2008)\textsuperscript{a}

\textsuperscript{a} Values are expressed as mean ± SD or (range); b Single dose; c Values expressed as mL/min/1.73m; d Steady state; e 12-h trough concentration; f eschar; g Values expressed as micrograms/gram; h values expressed as mean ± standard error of mean. Ad = adults; Ch = children; Cl = total body clearance; C\textsubscript{max} = maximum plasma concentration; C\textsubscript{trough} = trough plasma concentration; NA = no data available; t\textsubscript{1/2} = elimination half-life; TBSA = total burn surface area; TPB = time post-burn; UBS = unit burn standard Vd = volume of distribution.
1.8.3.2. Pharmacokinetic studies of cephalosporins in patients with burns

As with the penicillins, ceftazidime appears to have a greater volume of distribution, clearance and half-life, compared with non-burn patients (Walstad, Aanderud and Thurmann-Nielsen 1988). Other evidence indicates that there may be significant loss of ceftazidime through the burn wound (Zong, Xiao and Zhang 1994).

There is conflicting evidence on one other cephalosporin, cefepime. Whilst Bonapace et al (1999) reported a volume of distribution twice that of healthy subjects, and a slight increase in clearance, Sampol et al (2000) found no difference in these parameters. Both groups of investigators however agreed that the standard recommended dose for non-burn patients was sufficient.

The more recent publications of the use of cephalosporins in burns patients are by two French teams. Conil et al (2007a; 2007c) studied the factors that influenced the pharmacokinetics of ceftazidime. They found that clearances were likely to be higher for male patients, for patients who were not mechanically ventilated and for patients with higher creatinine clearances. They proposed that creatinine clearance (as estimated by the Cockcroft and Gault equation\(^6\) (Cockcroft and Gault 1976)) could be used to guide initial doses. They also found that volumes of distribution (in litres) were lower in men, and for non-ventilated patients. Their third paper that year (Conil et al. 2007d) concluded that with both ceftazidime and cefepime dose adjustments needed to take into account both age and creatinine clearance. Patients with creatinine clearances above 120ml/minute were thought to be particularly at risk of having sub-therapeutic serum concentrations.

Dailly et al (2003b) also examined the pharmacokinetics of ceftazidime in 41 adults with major burns. They noted that the volume of distribution was higher than in the study by Walstad et al (1988) and the total clearance was lower (Table 1.10). The differences were thought to be likely to be due samples being taken in the acute phase by Walstad, Aanderud and Thurmann-Nielsen (1988),

---

\(^6\) The Cockcroft and Gault Equation is \((140 – \text{age in years}) \times \text{bodyweight (kg)} / \text{serum creatinine (mmol/L)}. This figure is multiplied by 1.23 for males and 1.04 for females.
whereas their sampling took place after at least 48 hours i.e. in the hypermetabolic phase.

<table>
<thead>
<tr>
<th>Study details</th>
<th>Clearance (l/hr)</th>
<th>Volume of distribution (l/kg)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 patients in the acute phase</td>
<td>8.31</td>
<td>0.38</td>
<td>Walstad, Aanderud and Thurmann-Nielsen (1988)</td>
</tr>
<tr>
<td>41 patients in the hypermetabolic phase</td>
<td>2.72</td>
<td>10.61</td>
<td>Dailly et al (2003b)</td>
</tr>
<tr>
<td>50 patients in the hypermetabolic phase</td>
<td>4.03</td>
<td>0.30*</td>
<td>Conil et al (2007c)</td>
</tr>
</tbody>
</table>

* Mean volume of distribution (l/kg) was calculated from mean volume of distribution (l) / mean body weight (kg).

Table 1.10 shows the notable differences in the pharmacokinetic parameters calculated from three different studies of ceftazidime in patients with major burns.

1.8.3.3. **Pharmacokinetic studies of carbapenem antibiotics in patients with burns**

There were surprisingly few studies of the carbapenems in burns patients found in the literature review up to 2002. Whilst this group of antibiotics was relatively new then, they were often first choice for empiric treatment in life-threatening infections. Therefore ensuring maximal efficacy through undertaking pharmacokinetic studies would have been expected to be a priority.

Boucher *et al* (1990) noted a large inter-patient variability in the pharmacokinetic parameters of imipenem in burns patients, but overall no significant differences compared with healthy volunteers. However, they did note a correlation between imipenem clearance and creatinine clearance, suggesting that higher doses may be required for those with greater creatinine
clearances. More recently, Dailly et al (2003a) used a population pharmacokinetic approach to estimate pharmacokinetic parameters of imipenem in patients with burns. As with Boucher et al (1990) they found that renal function was the most likely factor to influence these parameters, and that higher doses may be required for patients with elevated creatinine clearance measurements. To confirm maximal efficacy, they recommended therapeutic drug monitoring of imipenem in this group of patients.

Yoshida et al (1993a) report serum concentrations of meropenem in Japanese patients at 1 hour to be 20 to 25mg/L following a dose of 1g. This is lower than would be expected from a healthy subject. Even lower 1 hour concentrations (8.8mg/L) were reported by Weinbren (1999) in a thirteen year old boy, who was given a dose 1.5 times the standard recommended maximum.

There have been further studies of the pharmacokinetics of meropenem. These are discussed in detail in Chapter 4.

1.8.3.4. Pharmacokinetic studies of other beta-lactam antibiotics in patients with burns

Friedrich et al (1991) demonstrated an increased volume of distribution with aztreonam, which correlated both with the albumin level and the extent of the burn injury. Despite these changes, the evidence available indicated that no change in dose was required for burns patients.

1.8.4. Pharmacokinetic studies of quinolones in patients with burns

Ciprofloxacin is probably the most used quinolone in severely burned patients, on the basis of cost and its spectrum of activity against Gram-negative bacteria. Both Metz et al (1989) and Garrelts et al (1996) reported a greater clearance and shorter half-life compared with healthy volunteers, with the recommendation that the drug is administered at a dose of 400mg every eight hours instead of the standard dose 400mg every twelve-hours. At this dose regimen, Garrelts et al (1996) found that the ratio of the area under the curve over 24 hours (AUC$_{24}$) of a serum concentration vs time plot to minimum
inhibitory concentration (MIC), the marker of efficacy for quinolones, was sufficient for 100% of organisms with an MIC for 0.125mcg/ml or less. This figure was only 63% for those with MICs of 0.25mcg/ml and with 0% for organisms with MICs of 0.5mcg/ml. As the MIC of one common burns pathogen, *P. aeruginosa* is sometimes higher than 0.5mcg/ml (Kojima, Inoue and Mitsuhashi 1989), higher doses than 400mg every eight hours may be needed if the antibiotic is being used to treat these bacteria. Lesne-Hulin *et al* (1999b) tested a dose of 600mg eight-hourly which was well-tolerated, but even this dose may still not be sufficient for patients with infections caused by organisms with high MICs.

Three other quinolones have been studied in burns patients. Enoxacin has been shown to have a peak serum concentration half of that expected for healthy volunteers (Van der Auwera *et al*. 1988), whereas it is thought there are no differences for ofloxacin (Potel *et al*. 1987; Sawada *et al*. 1993). Potel *et al*. (1987) found a substantial inter-patient variability in the pharmacokinetics of pefloxacin in burns patients, with the clearance and volume of distribution tending to be greater when the burn size was over 40% TBSA. A dose increase of 1.5 to 2 times the standard was recommended. Neither pefloxacin nor enoxacin are licensed in the UK.

More recently, Kiser *et al*. (2006) used the Monte Carlo simulation to evaluate levofloxacin in eleven patients with severe burns. All but one of the patients received a dose of 750mg once a day, with the other receiving 500mg once a day. In the UK, the recommended dose for skin and soft tissue infections is 500mg twice a day (BNF 2010). Levofloxacin pharmacokinetics in burned patients were found to be similar to those of other critically ill patients. Where MICs of infective Gram-negative organisms were 1mg/L or higher, it was proposed that either alternative treatment or doses higher than 750mg once a day would be required.
1.8.5. Pharmacokinetic studies of other antimicrobial agents in patients with burns

Another antibiotic, not licensed in the UK, fosfomycin showed a 1.5 to 2 times increase in both the volume of distribution and clearance compared with healthy volunteers, leading the investigators to conclude that the dosage should be doubled (Potel et al. 1989).

Fusidic acid is licensed in the UK, and may occasionally be used in patients with burns to treat staphylococci in combination with another antistaphylococcal agent. One study in patients with burns found fusidic acid clearance to be twice that of healthy subjects, together with a shorter half-life (Lesne-Hulin et al. 1999a). Despite this, the standard dosage of 500mg every eight hours was sufficient against organisms with an MIC of less than 2mg/L.

There is one abstract (Villarreal et al. 2000) describing the use of colistin against *P. aeruginosa* measured in five paediatric burn patients. Serum concentrations of colistin at steady state were measured using a microbiological assay. Four patients had a steady state concentration of 100mg/L and one patient 1mg/L. Efficacious and safe concentrations were determined to be 100mg/L or less, although there are different recommendations for this measure in the UK. More recent studies of colistin are discussed in Chapter 6.

There is also one publication (Mohr et al. 2008) relating to the use of daptomycin in patients with burns. Increases in volume of distribution and clearance, and decreases in peak serum concentrations, compared with healthy volunteers were noted, and it was calculated that patients with burns required almost double the dose to achieve the concentrations expected in healthy volunteers.

Up to 2002, there were no pharmacokinetic studies of linezolid, in patients with severe burns. In the absence of this data, standard doses were used in this group of patients. More recent studies relating to linezolid are discussed in Chapter 5.
1.9. Case study

In order to illustrate the principles of care described so far in this chapter, this section is a semi-fictional case study, based on a patient treated at the Queen Victoria Hospital for his burns in 2003. It particularly focuses on infection and its treatment.

Patient 1 (P1), a 30 year-old man, was admitted to a specialist burns centre from his local accident and emergency (A&E) department after sustaining a major burn. He had been rescued by fire fighters six hours previously from a house fire following a gas explosion. At the scene, ambulance crew covered his wounds with cling film to protect them and prevent evaporation. He was then taken to his local A&E department where he was assessed by an A&E registrar. On arrival he was reported to be alert and orientated, with a GCS (Glasgow Coma Scale) of 15/15, indicating full consciousness. His temperature was low at 35.5°C, oxygen saturations low, and he was tachypnoeic with a high respiratory rate of 35 breaths per min. The patient was tachycardic (high heart rate of 100 beats per minute), but his blood pressure was good at 150/80 mmHg. He was immediately administered oxygen, which improved his oxygen saturation and slowed his breathing rate. He was also given intravenous morphine to relieve his pain. There was no tenderness of P1’s pelvis or chest, and a chest x-ray showed no pneumothorax. Therefore no injuries other than his burn were suspected.

P1’s facial hair was singed, lips burned, oropharynx and tongue slightly swollen and carbon matter could be seen on his face, all signs of a possible inhalation injury. Although he was able to talk and his airways appeared to be clear, an endotracheal tube was inserted and P1 was ventilated. If this procedure had been delayed, it was possible that significant swelling would occur, making it very difficult to intubate. Following intubation, P1 was administered continuous infusions of an opioid analgesic and a sedative agent.

An arterial line was inserted into P1’s foot to enable the continuous measurement of blood pressure and to obtain samples for arterial blood gas measurements. He also had a central venous catheter (CVC) placed into his
left groin which allowed the administration of medicines, blood for testing and the measurement of cardiovascular data such as the central venous pressure. He was then given 2L of a crystalloid solution, which is part of the standard procedure for any major trauma patient, in order to maintain fluid volume. The patient had a catheter inserted into his bladder to allow the free-flow of urine and also the accurate measurement of urinary output and content. This aided with the assessment of the effectiveness of the resuscitation fluids and the functional status of the kidneys.

The burn was assessed, using the Lund and Browder chart (Figure 1.7) as about 35% of his total body surface area. Fluid requirements were calculated according to the Parkland Formula (Baxter and Shires 1968) as 4ml x 60kg x 35% = 8,600ml (see Section 1.4.1), although it is actually 8,400ml. Half of the volume, 4,300ml, needed to be administered by eight hours after the injury had occurred. As P1 had already received 2L of a crystalloid solution and approximately 1½ hours had elapsed since the explosion, over the next 6½ hours it was calculated that 2,300ml of crystalloid solution (Hartmann’s solution) would be required i.e. 350ml/hour.

P1’s wounds were left dressed with clingfilm, and he was re-covered with a blanket. Arrangements were made for transfer to the nearest burns centre.
Figure 1.7 Lund and Browder Chart completed for P1 in the admitting A&E Department

The chart was completed for P1 within an hour of his burn occurring. By shading the areas corresponding to the burn an estimate of the total percentage
area burn was made. Additionally, the chart provided other useful information for the receiving burns centre.

P1 suffered from paranoid schizophrenia, and had previously been “sectioned” twice. In the past he had made two suicide attempts and was known to have self-harmed. He was thought to have been better recently. His regular medication consisted of an antipsychotic and an antidepressant. P1 smoked 30 cigarettes a day, but took no other recreational drugs. He drank alcohol occasionally.

Following his arrival at the regional burns centre, and upon examination P1’s burn was reassessed to be 50%. The burns were mostly partial thickness and deep dermal, but full-thickness (1%) on the buttocks. His pulse was fast (120 beats per minute), and his blood pressure was low (105/55). This may have been due to the patient not receiving sufficient volumes of fluid, due to the under-estimation of the size of his burn. His fluid requirements were therefore recalculated. P1’s weight was now recorded as 63.2kg and it was six hours post-burn. Requirements were therefore 4ml x 50% x 63.2kg = 12,640ml in the first 24 hours. Half of this (6,320ml) should have been given in the first eight hours, and the other half in the next 16 hours.

Therefore by two hours’ time, P1 should have received 6.4L of intravenous fluid, but so far had only received 4L (3.5L crystalloid and 500ml colloid). He therefore would need another 1.2L per hour of Hartmann’s solution for the next two hours, then 400ml/hr for 16 hours.

The following plan was made:

1. Dressing change and further reassessment of burns.

2. Commence hourly nebulisers of salbutamol, acetylcysteine and sodium chloride 0.9% solution in case of inhalation injury. This would be
discontinued if bronchoscopy confirmed the absence of such injury (see Section 1.4.3).

3. Fluid requirements as above.

4. Intermittent positive pressure ventilation (IPPV) overnight with 50% oxygen i.e inflating the lungs intermittently through the endotracheal tube. This removes the work of breathing from the patient, so preventing exhaustion, improves carbon dioxide elimination, and may reduce oxygen requirements.

5. Naso-gastric feeding tube to be inserted and start feed (see Section 1.4.5).

6. Blood test
   • for full blood count (primarily to monitor the number of red and white blood cells and other blood constituents)
   • urea and electrolytes (primarily to monitor sodium and potassium levels, and also urea and creatinine levels to monitor hydration status and kidney function)
   • liver function tests
   • clotting screen
   • group and save (primarily to determine P1’s blood group and rhesus status).

7. Chest x-ray (see Section 1.4.3)

8. Physiotherapy to chest, to remove secretions and reduce the risk of respiratory infection occurring (see Section 1.4.3), and to limbs to maintain range of movement, and to limit muscle wasting (see Section 1.4.2 and 1.4.5).

9. Occupational therapist to apply splints to hands and elevate them (see Section 1.4.2).
10. Consultant to speak with P1’s parents and brother to explain the severity of injury, and the possibility of failure to survive.

Progress

Day 2

Bronchoscopy was performed, which gave a good view to the third generation bronchi, where the mucosa was pink, and no soot or debris seen. This indicated that there was no inhalation injury, and the nebuliser regimen was stopped.

During the first dressing change, the burns were photographed (Figures 1.8a and b) and a reassessment of the burn area indicated that it was actually 70% TBSA, 10% of which was full-thickness. Burns were to the head, arms, left hand, right leg and some areas of the left leg (all partial thickness), right hand (full-thickness), torso (partial thickness, deep dermal and full thickness), back (deep dermal), and flanks and buttocks (full thickness) (see Section 1.2.1). P1 required fluid boluses (a large volume given quickly) on top of the infusion to maintain his blood pressure, urine output (at least 0.5ml/kg/hour) and haematocrit at normal levels.

At this first dressing change, Flammacerium®, an antimicrobial cream (see Section 1.5.4) was applied to the deep burns. All wounds were then covered with paraffin gauze to prevent an outer layer of cotton wool / gauze from sticking to the wound. The cotton wool / gauze was used to absorb the burn exudate.
Figure 1.8a First inspection of the upper body at the Burns Centre

The burn areas are the darker patches. The patient is oedematous, especially the face and the scrotum.

Figure 1.8b First inspection of the lower limbs at the Burns Centre

Burns were sustained to most areas of the legs, but the feet were largely unburned due to protections from socks.
Day 3

P1 was taken to the operating theatre for a total excision of his burn wound. Immediately before commencement, co-amoxiclav was administered intravenously as antibiotic prophylaxis against staphylococcal and anaerobic bacteria. The wounds were first infiltrated with a weak adrenaline solution to reduce bleeding. Then, all full-thickness and partial-thickness burns were debrided (removal of dead, damaged and/or infected tissue) before covering with a skin graft. It was possible to use some of the left leg as a donor site for harvesting skin graft tissue. This was widely meshed (4:1) to cover the back, which then had meshed (2:1) allograft (cadaveric skin) placed on top. The other areas were covered in meshed allograft only. The wounds were then covered with a non-shear dressing, paraffin gauze and finally a cotton wool/gauze dressing. Additionally, a skin sample was taken from the left leg for culturing of keratinocytes, which would take two to three weeks. During the surgery P1 required ten units of blood, six units of fresh frozen plasma, and platelets.

Days 4 to 15

P1 remained stable. His blood results were relatively normal, except for a low albumin level of between 10 and 15g/L, (normally 35 – 50g/L) and low haemoglobin of around 9g/dL (normal range 14 to 17 for a healthy man) which would be expected to be seen in a patient with a major burn. His blood sugar levels increased, an indication of the hypermetabolic response. He was commenced on an insulin infusion to maintain blood sugar levels to within the normal range.

He continued to be ventilated and sedated and received twice daily chest physiotherapy. The occupational therapist applied splints to his hands to prevent wound contracture, and to keep them elevated. Both the physiotherapist and occupational therapist worked on P1’s general movement to maintain a good range of motion.
Dressings were repadded daily. A full dressing change was required on day 6 post-injury, with dressings being removed down to, but not including, the non-shear dressing. This enabled an inspection of the graft and allowed the removal of any haematomas (leakage of blood from the blood vessels).

On post-burn day 8, the non-shear dressing and staples were removed. The wound was then showered with tap water to reduce bacterial colonisation, and redressed. Dressing changes were undertaken every two to three days thereafter. At every dressing change the wounds were scrubbed to reduce their bacterial count.

Isolates from wound swabs initially grew *S.aureus*, but after a few days *P.aeruginosa* was also isolated.

**Day 16**

P1’s allograft was being rejected. The area grafted on his back appeared to be healing, as well as the donor site on his leg, but neither was fully healed. As no further autograft skin could be used for grafting, P1 was taken back to the operating theatre for further application of allograft to all areas.

**Day 17**

P1 had developed tachycardia and pyrexia (high temperature) and had difficulty maintaining his blood pressure – signs of SIRS or sepsis (see 1.4.1) - for which noradrenaline was administered as a continuous intravenous infusion. He also had the “short Synacthen® test” to test for cortisol concentrations (see 1.4.1). Hydrocortisone and fludrocortisone were commenced, both of which were to be stopped if the test indicated that cortisol levels were normal. If levels were low, the steroids were to be given for at least seven days, before considering stopping the fludrocortisone and tailing off the hydrocortisone over a further three-day period.

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7 Noradrenaline is an inotrope which increases myocardial contractility, and is used to support cardiac function when blood pressure is low.
P1’s platelets and haemoglobin remained low, and he had also developed abnormal clotting with an APTT ratio, a measure of the blood’s ability to clot, of 2.4 (normal value about 1.0) for which he was given fresh frozen plasma. He began to have difficulties absorbing his feed and was commenced on a gut motility agent. His temperature was 39.1°C and his white cell count had quickly increased to 23.3 x 10^9/L. His chest x-ray showed fluid at the base of the lungs, and shadowing indicating inflammatory tissue. His oxygen requirements had increased and more respiratory support was required. All these signs indicated a respiratory tract infection, and a full set of wound swabs were taken (wound, blood, sputum, urine and CVP tip). The *Pseudomonas aeruginosa* that had been identified from previous wound swabs was sensitive only to piperacillin / tazobactam, meropenem and colistin, and the microbiologist advised to commence the piperacillin / tazobactam combination. The dose prescribed was 4.5g every six hours, which was more frequent than the usual eight-hourly dosing, but in line with the recommendation in patients with major burns (Bourget *et al.* 1996).

**Day 18**

P1’s noradrenaline requirements were increasing and his chest x-ray indicated lung collapse.

The consultant microbiologist reported the presence of *P. aeruginosa* isolated from the sputum, and from wound swabs, but no growth from the other specimens. Meticillin-resistant *Staphylococcus aureus* (MRSA) and *Acinetobacter baumannii* were also isolated from wound swabs. Susceptibilities to these organisms are outlined in Table 1.11. The microbiologist gave advice to stop treatment with piperacillin / tazobactam and start with intravenous meropenem at the standard maximum dose of 1g eight-hourly. If there continued to be no improvement in P1’s condition, he advised to add vancomycin as a continuous infusion to the meropenem therapy.

Dressing changes were increased to daily to reduce P1’s temperature, and to try to decolonise the wound.
<table>
<thead>
<tr>
<th>Site</th>
<th>Pathogen(s) identified</th>
<th>Sensitive to</th>
<th>Resistant to</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound</td>
<td>P. aeruginosa</td>
<td>Mer, Col</td>
<td>Pip/taz, Cef, Gent, Cip</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mer, Pip/taz, Cef, Gent, Cip</td>
</tr>
<tr>
<td></td>
<td>A. baumannii</td>
<td>Col</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MRSA</td>
<td>Vanc, Rif, Fus, Tet</td>
<td>Fluc, Eryth, Cip</td>
</tr>
<tr>
<td>Sputum</td>
<td>P. aeruginosa</td>
<td>Mer, Col</td>
<td>Pip/taz, Cef, Gent, Cip</td>
</tr>
<tr>
<td>Blood</td>
<td>No growth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine</td>
<td>No growth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVP Tip</td>
<td>No growth</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1.11 Pathogens isolated from sites at day 17 post-injury and their reported susceptibilities

Table 1.11 shows the pathogens identified from P1 taken on day 17, together with the susceptibilities reported. Cef = ceftazidime, Cip = ciprofloxacin, Col = colistin, Eryth = erythromycin, Fluc = flucloxacillin, Fus = sodium fusidate, Gent = gentamicin, Mer = meropenem, Pip/taz = piperacillin/tazobactam, Rif = rifampicin, Tet = tetracycline

Day 20

On the morning ward round, P1’s antibiotic therapy was reviewed. There had been little improvement in his condition during the previous 48 hours. The decision was made to continue with meropenem, but also to start a continuous intravenous infusion of vancomycin to treat the MRSA, as previously advised by the consultant microbiologist.

As P1 was under 60 years old, he was given a vancomycin loading dose of 1.5g, then commenced on a dose of 40mg/kg/day, rounded off to the nearest 500mg (Table 1.12). This dose was based on the findings from a pharmacokinetic study which found that a higher than normal dose was required in burns patients in order to achieve therapeutic serum concentrations (Conil et al. 1994) (see Section 1.8.2)
<table>
<thead>
<tr>
<th>Day post-burn</th>
<th>Dose (g/24 hours)</th>
<th>Serum concentration (mg/L)</th>
<th>Dose change (g/24 hours)</th>
<th>Serum creatinine (μmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>2.5</td>
<td>-</td>
<td>Starting dose</td>
<td>54</td>
</tr>
<tr>
<td>21</td>
<td>2.5</td>
<td>13.7</td>
<td>Increase to 3.0</td>
<td>62</td>
</tr>
<tr>
<td>22</td>
<td>3.0</td>
<td>18.6</td>
<td>No change</td>
<td>55</td>
</tr>
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</tr>
<tr>
<td>24</td>
<td>3.0</td>
<td>29.1</td>
<td>Decrease to 2.5</td>
<td>115</td>
</tr>
<tr>
<td>25</td>
<td>2.5</td>
<td>24.4</td>
<td>Decrease to 2.0</td>
<td>106</td>
</tr>
<tr>
<td>26</td>
<td>2.0</td>
<td>18.2</td>
<td>No change</td>
<td>103</td>
</tr>
<tr>
<td>27*</td>
<td>2.0</td>
<td>16.0</td>
<td>No change</td>
<td>85</td>
</tr>
<tr>
<td>28</td>
<td>2.0</td>
<td>11.4</td>
<td>Increase to 2.5</td>
<td>72</td>
</tr>
<tr>
<td>29</td>
<td>2.5</td>
<td>15.6</td>
<td>Increase to 3.0</td>
<td>54</td>
</tr>
<tr>
<td>30</td>
<td>3.0</td>
<td>-</td>
<td>Vancomycin stopped</td>
<td>62</td>
</tr>
</tbody>
</table>

Table 1.12 Serum concentrations and dose adjustments required for effective vancomycin treatment (target 15 to 25mg/L)

The table illustrates the fluctuations in serum concentrations of vancomycin when administered as a continuous infusion. Of note is the increase in serum concentrations, and hence decreased dosage requirements, with the increase in creatinine concentrations.

* Vancomycin was stopped on day 27, but recommenced later that day. The patient was reloaded with a dose of 1g, and then recommenced at the previous dose of 2g in 24 hours.

Day 21

The vancomycin serum concentration was reported to be 13.7mg/L which was below the recommended range in local guidelines of 15 to 25mg/L. The dose was therefore increased to 3g over 24 hours.

Day 22

On the ward round it was reported that P1 had been unstable for the previous 48 hours, with raised temperature and white cell count, and increased noradrenaline requirements to maintain his blood pressure, but was settling
now. His noradrenaline requirements had decreased, his white cell count was returning to normal, his temperature had reduced to 38.0°C.

Day 24

P1’s serum vancomycin concentration was above the therapeutic range at 29.1mg/L. His serum creatinine had also increased to 115micromol/L. The dose was reduced back to 2.5g/24 hours.

Day 25

P1’s condition continued to generally improve:

- He was still dependent on noradrenaline but the dose has been coming down slowly
- He was still ventilated. He required positive end-expiratory pressure (PEEP), a continuous pressure to the lower airways at the end of the breathing cycle, so preventing the alveoli from collapsing.
- His chest was clinically clear, indicating the absence of a respiratory infection.
- His gut was working well (see Section 1.4.5) and his feed was being absorbed. However he had diarrhoea. For this reason a stool sample was taken and sent to be tested for Clostridium difficile. This is an organism that causes diarrhoea and other intestinal disease when competing bacteria are killed as a consequence of antibiotic therapy.
- There was good urine output, indicating he was receiving adequate fluids and his kidneys were working adequately.
- Blood results were generally encouraging, although his plasma sodium concentrations high at 158 mmol/L (see Section 1.4.5). His creatinine was still raised indicating some degree of renal impairment, and his C-reactive protein (an indication of inflammation and/or infection) was raised. He was to receive two units of blood that night as his haemoglobin was 8.7g/dL (normal range 13 to 18 in men) and further surgery was planned for the following day. His albumin was up to 16g/dL (see Section 1.3), although this was still low compared with the range in
healthy subjects (35 to 40g/dL). His white cell count, platelets and clotting were all returning towards normal.

P1 had now received 5 days of vancomycin treatment and seven of meropenem. As surgery was planned for the following day, it was decided to continue with them for two more days. P1’s serum creatinine was still raised (106 μmol/L), indicating some degree of renal impairment. As nephrotoxicity was a recognised potential side-effect of vancomycin (BNF 2001), the dose was reduced further, from 2.5g to 2g over 24 hours. It was hoped that at this dose, the serum concentration would remain above 15mg/L as it had been at the higher end of the range (24.4mg/L).

**Day 26**

P1 went back to theatre for further grafting. The donor site on his leg had fully healed, so could be reused and the cultured keratinocytes were also ready for use.

**Day 27**

P1 had continued to improve. Antibiotics were stopped as planned, and new swabs taken. However P1 became more unsettled during the day. It was decided to restart the meropenem and vancomycin. The consultant microbiologist reported scanty *Candida albicans* in the sputum and fluconazole was also commenced on the presumption that the fungus might be infective rather than just colonising the sputum. The standard recommended dose for this indication, 400mg once a day, was prescribed, despite evidence that higher doses may be required to achieve concentrations comparable with those of healthy volunteers (Boucher *et al.* 1998).

It was also noted that serum creatinine had come down to 85micromol/L, indicating an improvement in renal function.
Day 28

Vancomycin serum concentrations were below therapeutic range, at 11.4mg/L. The dose was therefore increased back from 2g/24 hours to 2.5g/24 hours.

Day 29

P1 had become more hypotensive over the previous two days, and hence his noradrenaline requirements had increased. Adrenaline had been introduced, but had little effect, so he was commenced on furosemide and dopamine to reduce his positive fluid balance. He was dependent on PEEP and had poor gas exchange. Arterial blood gas analysis showed a low partial pressure of oxygen in arterial blood (PaO$_2$), despite receiving 50% oxygen. A review of his chest x-ray led to the diagnosis of sepsis and acute respiratory distress syndrome (ARDS) (see Section 1.4.3).

At the increased dose of 2.5g/24 hours, vancomycin serum concentrations were 15.6mg/L. P1’s serum creatinine concentration was now 54micromol/L which was similar to values before vancomycin had commenced. As the vancomycin was only just in therapeutic range, it was decided to increase the dose to 3g/24 hours.

Day 30

There was little improvement in P1’s condition. The microbiologist reported that Acinetobacter baumannii had been grown from the most recent blood culture which was resistant to all antibiotics, except for colistin (Table 1.13). As the patient’s renal function had appeared to have returned to that of before vancomycin therapy, it was decided to stop the meropenem and vancomycin, and to commence colistin. Fluconazole was continued.
<table>
<thead>
<tr>
<th>Site</th>
<th>Pathogen(s) identified</th>
<th>Sensitive to</th>
<th>Resistant to</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound</td>
<td><em>P.aeruginosa</em></td>
<td>Mer, Col</td>
<td>Pip/taz, Cef, Gent, Cip</td>
</tr>
<tr>
<td></td>
<td><em>A.baumannii</em></td>
<td>Col</td>
<td>Mer, Pip/taz, Cef, Gent, Cip</td>
</tr>
<tr>
<td>Sputum</td>
<td><em>P.aeruginosa</em></td>
<td>Mer, col</td>
<td>Pip/taz, Cef, Gent, Cip</td>
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<tr>
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<td><em>A.baumannii</em></td>
<td>Col</td>
<td>Mer, Pip/taz, Cef, Gent, Cip</td>
</tr>
<tr>
<td>Urine</td>
<td>No growth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVP Tip</td>
<td>No growth</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Table 1.13 pathogens isolated and their susceptibilities Day 30*

Table 1.13 shows the pathogens identified from P1 taken on day 30, together with the susceptibilities reported. Until this set of samples, no pathogens had been grown from blood samples. MRSA had been eradicated from the wound indicating the effectiveness of the vancomycin therapy. Amp = ampicillin, Cef = ceftazidime, Col = colistin, Eryth = erythromycin, Fluc = flucloxacillin, Fuc = sodium fusidate, Gent = gentamicin, Mer = meropenem, Pip/taz = piperacillin/tazobactam, Rif = rifampicin, Tri = trimethoprim

The prescribed dose of colistin was the standard recommended dose of 2 megaunits eight-hourly. It was decided to measure a “peak” serum concentration after 2 days of treatment, in order to determine whether P1 was receiving an appropriate dose. As colistin is known to cause nephrotoxicity (see Chapter 6), the patient’s renal function was to be monitored by daily creatinine clearance measurements.

**Day 32**

P1’s condition continued to deteriorate, although his renal function remained stable. A serum sample was sent off to determine the concentration of colistin.
A change of dressing under general anaesthetic concluded that only a few areas were healing well. To aid wound healing, an anabolic steroid, oxandrolone, was commenced.

**Day 33**

The consultant anaesthetist concluded that there was real evidence of septicaemia. Peaks and troughs in temperature, white cell count and C-reactive protein were seemingly unrelated to antibiotic regimen and more closely matched to theatre and dressing change days.

**Day 35**

The colistin peak serum concentration was reported to be 9mg/L. As local guidelines stated the target range to be 10 to 15mg/L, the dose was increased to 2.5mU every eight hours.

**Day 37**

P1’s condition had been largely unchanged for a week, although he was less oedematous. It was noted that there had been blood in the patient’s aspirate, which was thought may have been caused by the tracheostomy tube that had been inserted. Intravenous ranitidine was commenced to reduce gastric acid output in the stomach, in case the blood was due to a gastro-intestinal bleed.

**Day 38**

P1 was reported to be “less well”. He continued to require respiratory, circulatory and renal support.

The most recent laboratory cultures isolated from the various sites continued to detect *P. aeruginosa* from the burn wounds, but *A. baumannii* and MRSA were no longer present. However, coagulase negative staphylococci were now
identified. Sputum samples revealed *P. aeruginosa* and *S. maltophilia* (Table 1.14)

<table>
<thead>
<tr>
<th>Site</th>
<th>Pathogen(s) identified</th>
<th>Sensitive to</th>
<th>Resistant to</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound</td>
<td><em>P. aeruginosa</em></td>
<td>Mer, Col</td>
<td>Pip/taz, Cef, Gent, Cip</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CNS</td>
<td>Fluc, Mer, Pip/Taz, Cef</td>
</tr>
<tr>
<td>Sputum</td>
<td><em>P. aeruginosa</em></td>
<td>Mer, col</td>
<td>Pip/taz, Cef, Gent, Cip</td>
</tr>
<tr>
<td>Blood</td>
<td></td>
<td>S. maltophilia</td>
<td>Co-trimoxazole</td>
</tr>
<tr>
<td>Urine</td>
<td>No growth</td>
<td>No growth</td>
<td></td>
</tr>
<tr>
<td>CVP Tip</td>
<td>No growth</td>
<td>No growth</td>
<td></td>
</tr>
</tbody>
</table>

*Table 1.14 pathogens isolated and their susceptibilities from Day 37*

Table 1.14 shows the pathogens identified from P1 taken on day 37, together with the susceptibilities reported. CNS and *S. maltophilia*, although not previously isolated, were unlikely to be pathogenic. Cef = ceftazidime, CNS = coagulase negative staphylococci, Col = colistin, Gent = gentamicin, Mer = meropenem, Pip/taz = piperacillin/tazobactam

It was agreed to stop the colistin and fluconazole, as they had been given for over a week, but to restart meropenem. This time it was decided to use a higher dose, in case the reason for previous treatment failure was due to altered pharmacokinetics resulting in sub-therapeutic concentrations. A dose of 2g eight-hourly was selected, as this was the licensed dose recommended for patients with cystic fibrosis. The microbiologist advised that *S. maltophilia* and CNS were unlikely to be pathogenic.

**Day 39**

Further deterioration was reported over the previous 24 hours. P1 was unstable overnight and had to be paralysed on atracurium for several hours in response to fluctuating sedation and discoordinate ventilation with resultant haemodynamic compromise.
P1’s problems could be summarised as:

- Persisting sepsis / inflammatory state on high dose meropenem, but no obvious response to antimicrobial therapy.
- No further healing of wounds over past week evident, likely to be due to the presence of infection.
- Significant continuing exudative fluid loses from the burns wounds, indicating inflammation and infection.
- Cardiovascular system deterioration after dressing change today. His heart rate had increased, and blood pressure, urine output, core and peripheral temperature had all dropped. The rates of noradrenaline and dopamine had been increased, but with little effect. Careful fluid loading was therefore suggested in order to maintain blood pressure.
- Lung injury (ARDS), which was influenced by respiratory depression caused by opioid analgesia. It was agreed to try methadone, another opioid analgesic, to see if it had less of a respiratory effect, and to keep morphine and midazolam rates down.
- Blood had been identified in faeces as well as the aspirate, further indicating a gastro-intestinal bleed. Treatment with omeprazole, a proton pump inhibitor, replaced that of ranitidine, as it was thought to be more effective in inhibiting gastric acid production. Additionally, sucralfate was administered, which is thought to protect the gastric mucosa. Because of the blood loss, four units of blood were transfused.
- Metabolically stable
- Absorbing feed

The consensus amongst medical staff was that the prognosis looked poor, and that the relatives were to be informed of this. Current support could be escalated but further options were limited.

**Day 40**

P1 deteriorated overnight. He had poor urine output and now had increasing creatinine (178micromol/L), both indicating renal impairment. His blood
pressure was low, and heart rate high, despite maximum inotropic support. He was felt to be in a terminal phase. It was decided to commence dopexamine, which acts on peripheral dopamine receptors to increase renal perfusion. If this did not improve renal function, consideration was to be given to withdrawing inotropic support, and for P1 to receive only palliative therapy.

Later that day, it was noted that the dopexamine had had no effect on the kidneys. It was agreed that active treatment would be withdrawn and P1 died at 15.02.

**Discussion**

This case illustrates some of the difficulties of infection management in patients with major burns, and uncertainties relating to the dosage of antibiotics. P1, age thirty years, had what was eventually agreed to be a 70% TBSA burn. He therefore had a Baux index of 100, indicating that prognosis was poor. His ABSI score was 10, and making his probability of survival 0.2 to 0.4. As with many severely burned patients, he deteriorated over a period of weeks, before succumbing to multi-organ failure caused by sepsis. His antibiotic therapy is summarised in Figure 1.9.

For the first two weeks post-burn, P1 was relatively stable. Whilst the burn wounds became colonised (see Section 1.5.2), there was no indication of infection. However, he then deteriorated, showing signs of sepsis. Empirical therapy was commenced, but guided by susceptibilities of organisms isolated from wound swabs. The high dose of the first antibiotic used, piperacillin with tazobactam, was determined in a pharmacokinetic study in patients with severe burns (Bourget et al. 1996).

*P. aeruginosa* was then isolated from sputum, and symptoms indicated the presence of a respiratory infection. *P. aeruginosa*, MRSA and *A. baumannii* were isolated from wound swabs. As P1’s condition was deteriorating, the piperacillin/tazobactam was discontinued, because of the reported resistance of the *P. aeruginosa* to it, and instead meropenem was commenced.
* Meropenem and vancomycin were stopped on day 27, but recommenced later that day.

** Dose of colistin increased on day 35 to 2.5MU eight-hourly following reported low “peak” serum concentrations

Figure 1.9. Summary of antibiotic treatment for P1
In the absence of adult dosage guidelines in patients with burns, the usual dose of 1g every eight hours of meropenem was selected. Despite this, the meropenem had little effect, which may have been due to the infection being caused by organisms that had not been isolated which were not susceptible to meropenem, or it may have been due to a consequential sub-therapeutic dose of meropenem being used. A higher than usual dose of meropenem is recommended for patients with cystic fibrosis (AstraZeneca 2010). Patients with cystic fibrosis are known to have altered pharmacokinetics, and as with patients with burns, often require higher than usual doses for drug therapy to be effective (Kearns, Hilman and Wilson 1982; Prandota 1988; Lindsay and Bosso 1993). P1 was a young man with good renal function at the time, so it was likely that he would have tolerated a higher dose. The only drawback therefore would have been the additional cost of therapy. Meropenem is discussed in more detail in Chapter 4.

Although *A.baumannii* was isolated from wound swabs, it was not found in the sputum. Even if it had been, *P.aeruginosa* would have been much more likely to be the cause of the infection. Meropenem was selected over colistin to treat the *P.aeruginosa* as it is well tolerated, and there is a general reluctance to use colistin, because of its reputation as a toxic antibiotic. For this reason it is usually reserved for the treatment of susceptible organisms that are resistant to all other antibiotics. Additionally in this case it would have meant that two nephrotoxic drugs – colistin and vancomycin - were used at the same time, potentially increasing the risk of the development of renal impairment. Colistin is discussed in more detail in Chapter 6.

Vancomycin was selected to treat the MRSA because it was the first line antibiotic in the Trust medicines formulary for this indication. It was thought to be a good antibiotic to select for P1 because pharmacokinetic studies had resulted in dose recommendations for patients with severe burns (Conil *et al.* 1994), and it is routine practice in all patients to measure serum concentrations to ensure a therapeutic dose. Therefore dose adjustments could be made if concentrations were above or below the recommended range. Other
intravenous antibiotics effective against MRSA that were available at the time included linezolid and teicoplanin. Results of one study had indicated that higher than usual doses of teicoplanin should be used in patients with major burns (Steer et al. 1996) with the recommendation of monitoring serum concentrations. Such monitoring is practically more difficult to undertake than with vancomycin. With linezolid there were no guidelines for dosage in patients with burns, and facilities for the monitoring of serum were not easily accessible. There is however evidence that linezolid has good penetration into skin and soft tissues (Gee et al. 2001), and a reduction in length of stay has been shown compared with vancomycin for patients with complicated skin and soft tissue infections from suspected or confirmed meticillin-resistant staphylococci (Li et al. 2003d). Therefore, if dosing recommendations had been available for linezolid in patients with burns, this may have been a better choice of antibiotic. Linezolid is discussed in more detail in Chapter 5. P1’s condition improved after the commencement of vancomycin, and MRSA was eradicated from the wound swabs.

The serum concentrations of vancomycin clearly indicate how dosage requirements are affected by pathophysiological changes that occur with a major burn. Non-burn patients rarely require doses above 2g in 24 hours, but whilst P1’s renal function was good, he required 3g over 24 hours to reach therapeutic serum concentrations. A known adverse effect of vancomycin is nephrotoxicity (BNF 2010), and vancomycin may have been the cause of the rise in serum creatinine.

It was not clear whether there was a slow response to the meropenem, or if the cause of infection was a Gram-positive organism that was responsive to the vancomycin. However, when the meropenem and vancomycin were discontinued, the patient deteriorated. Both antibiotics were therefore recommenced. Additionally fluconazole was prescribed as the C.albicans isolated in the sputum may have been infective. Whilst there was some evidence to suggest that the pharmacokinetics of fluconazole is altered in patients with burns (Boucher et al. 1998; Pittrow and Penk 1999; Rayatt,
Wienbren and Clarke 2000) no higher dose recommendations had been made. Therefore the dose selected was at the top end of the licensed dose range.

Three days after the fluconazole commenced, P1 had shown no improvement. Colistin was commenced, as it was the only antibiotic that the A. baumannii was susceptible to. This meant meropenem could be stopped, as colistin would provide Gram-negative cover, particularly against P. aeruginosa. It was also decided to stop the vancomycin again, as P1 had received almost continuous treatment for ten days. Like vancomycin, colistin can also cause renal toxicity (BNF 2001). Therefore stopping the vancomycin avoided concomitant use with colistin so reducing the risk of nephrotoxicity.

Colistin is discussed in detail in Chapter 6. In the absence of any other guidance in burns patients, the standard dose was selected. It was five days before the “peak” serum concentration was reported to be below the target range of 10 to 15mg/L. This was because treatment was commenced on a Saturday, and samples could be processed on only a weekday. Additionally the microbiological assay used for colistin takes 48 hours. Therefore P1 had been receiving a sub-therapeutic dose of colistin to treat septicaemia for almost a week. There is evidence to suggest with aminoglycosides that late attainment of therapeutic serum concentrations is associated with increased mortality in patients with Gram-negative bacteraemia (Moore, Smith and Lietman 1984), and this may be the case with other antimicrobial agents. Additionally, sub-therapeutic doses may have increased the risk of development of resistance of the A. baumannii, potentially leaving it susceptible to no antibacterial agent. This highlights the need for dose guidelines in burns patients to increase the chances of achieving therapeutic concentrations from the start of treatment. On receipt of the peak serum concentration measurement, the dose of colistin was increased, and the next set of cultures indicated eradication of the A. baumannii.

The reintroduction of meropenem at an increased dose had little positive effect. P1 was deteriorating and it is possible that by this stage no antimicrobial therapy could be effective. With better knowledge of the pharmacokinetics of the antimicrobials, earlier infections may have been treated more effectively.
This could have prevented the development of multi-organ failure, and the final outcome may have been different.

Of note is the observation that peaks and troughs in temperature, white cell count and C-reactive protein were seemingly unrelated to antibiotic regimen and more closely matched to theatre-days and dressing-change days. This is commonly reported in patients with burns (Piel et al. 1985; Ljunghusen et al. 1995). It is thought to be due to the scrubbing of the burn wound disturbing bacteria from the colonised wound, so entering the blood stream. It tends to occur one to two hours after the procedure, and may often last only a few hours. However, it may also predispose to episodes of surgically-induced sepsis. Subtherapeutic dosing of antibiotics may increase the chances of this occurring.

This case illustrates the need for more pharmacokinetic data on antibiotics used in order to develop guidelines for the treatment of infections in severely burned patients. Such guidance will give the clinician the confidence to conclude that if a patient is not responding to antimicrobial therapy, it is not because of subtherapeutic dosing, but because the infection is caused by a different, non-susceptible organism. If dosage guidelines had been available for all of the antibiotics used for P1, his chance of survival may have been greater.

1.10. Summary

Major burn injury is one of the most devastating forms of trauma. It can affect almost every organ of the body and, despite significant advances over the last few decades, remains life-threatening. Infection is a major cause of death in these patients, due to ease of systemic access of microbes and the immunocompromised state of the patient. It is therefore crucial that any antimicrobial therapy targets the causative organisms and is administered in effective doses. Pathophysiological changes that occur with a major burn have been shown to affect the pharmacokinetics of many antibiotics resulting in higher dose requirements to achieve maximal efficacy. However, there are several antibiotics where data is lacking, leaving the clinician unable to be confident that the doses used are sufficient to treat these life-threatening infections. Studies of these antibiotics in such patients are required to produce
dosing recommendations. This will avoid the concern that morbidity and mortality are related to sub-therapeutic dosing.

1.11. Aims and Objectives

Aims

• To identify antibiotics used to treat infection in critically ill patients with burns in the UK, where dosage guidelines are conflicting or lacking.
• Where pharmacokinetic data are lacking, to investigate the pharmacokinetic parameters of antibiotics when administered to patients with major burns and to produce dosing guidelines for the use of these antibiotics.
• Where pharmacokinetic parameters are published, to review the appropriateness of current dosage guidance.

Objectives

• To conduct a survey of antimicrobial use in burns centres in the UK.
• To use the survey to identify antimicrobial agents used to treat severe infections in the UK where data is either conflicting or lacking.
• To measure the serum concentrations of antimicrobials where little or no pharmacokinetic data are available in adults with major burns (>15% total body surface area) receiving these antibiotics for treatment of severe infections.
• To compare the serum concentrations with those required to treat likely infections.
• To calculate pharmacokinetic parameters such as volume of distribution, clearance and elimination half-life.
• To compare pharmacokinetic parameters calculated in this study of severely burned patients with other populations.
• To investigate the influence of patient factors on the serum concentrations and pharmacokinetic parameters.
- To produce dosage guidelines for the use of these antibiotics in adults with major burns.
- For antimicrobials where pharmacokinetic data are published, to review current dosage guidelines and to use local data to illustrate the use of the guidelines in practice.
- To ascertain, using the data generated by the study and that previously published, whether there is a model for the dosing of all antibiotics in burns patients.
Chapter 2. Use of antimicrobial agents in burns centres the UK

2.1. Introduction

In order to aid with the decision of which antibiotics were to be studied in detail, a survey was conducted on drug use in burns centres in the UK in 2001 (Allen et al. 2002). This was repeated in 2009 to determine any changes in current practice. Additionally, the later survey would enable the identification of any new work required in this area. The criteria for the selection of antimicrobials for further investigation were antibacterial agents (i) that were generally reserved for the treatment of infections in critically ill patients, (ii) where there were no, or limited, dose recommendations published for patients with major burns and (iii) for practical reasons, they needed to be in use at the base study site, the Queen Victoria Hospital in East Grinstead.

2.2. Method

The 2001 questionnaire concerned use of drugs generally (Appendix 1). The primary aim was to determine how practice varied between different units. However it included detailed questions relating to antimicrobial therapy, relating to choice of antimicrobial, indications and frequency of use. It was piloted, amendments made and then sent to the lead pharmacist for burns care at each UK site. Twenty-three surveys were sent. Non-responders were resent the questionnaire with a covering letter.

The 2009 questionnaire related only to antimicrobial use (Appendix 2). In addition to the questions in 2001, it also ascertained data relating to dosing and monitoring. It was designed, piloted, and amendments made. Sixteen questionnaires were posted out. The number was lower than in 2001, as it was sent to only those units which treated major burns patients. Non-responders were followed up by telephone and email. To further increase the response rate, the survey was then put into a web-based format (www.surveymonkey.net) and sent out again.
2.3. Results

The results primarily refer to the 2009 survey as this related solely to the antimicrobial use, and reflects current practice. However, data is presented for the first survey where appropriate.

After follow up, the response rate for the 2001 survey was 65% (fifteen responses), of which all but one answered the questions relating to choice of antimicrobials. After follow up by email and phone, the response for the 2009 survey was 44% (7 questionnaires). This doubled to 88% (14 questionnaires) when sent electronically, of which 13 (81%) were completed fully.

In the 2009 survey, four of the hospitals had dedicated burns intensive care units (ICUs). Five more treated burns on a general ICU, and one treated patients on both a dedicated and a general intensive care unit. The question of where patients were treated was not answered by the other responders. The number of patients that could be treated in the dedicated burns ICUs ranged from 1 to 5 (mean 2.8), whereas trusts with general ICUs could treat between 4 and 75 patients (mean 23). The mean number of high dependency unit beds\(^8\) were 2.9 (range 1 to 6), although one trust could treat another 15 on the general critical care unit.

One respondent was a consultant burns surgeon. All of the others were pharmacists. Respondents had been qualified for a mean of 13 years (range 2 to 23), and worked with burns patients for a mean of 4.7 years (range 1 to 15). No respondent spent over 40% of their week working either directly with burns patients or on burns-related issues.

There were changes in the antibiotics that were used in 2009 compared with 2001. It can be seen in Figure 2.1 that in 2001, no single antimicrobial was used by all units. Seven years later, there were five; fluconazole (57% in 2001),

\(^8\) Patients treated on the HDU are generally not as severely ill as those requiring intensive care, but needing more input than a general ward. Most burns centres with ICUs will also have HDUs.
meropenem (50%), metronidazole (79%), a quinolone (71%) and piperacillin with tazobactam (64%).

There were also notable increases in the number of units using amikacin (21% to 62%), amphotericin (43% to 69%), clindamycin (36% to 77%), colistin (7% to 46%), linezolid (14% to 77%) and vancomycin (57% to 85%). Additionally four units now used daptomycin, and three tigecycline, both of which were not available in 2001.

In 2001, 57% of units used imipenem, which dropped to 15% in 2009. Similarly there were notable reductions in cefotaxime (64% to 23%), chloramphenicol (21% to 0%), co-trimoxazole (36% to 8%), piperacillin alone (14% to 0%) and Synercid® (21% to 0%).

In 2009, three units had antimicrobial guidelines specific to burns, and one more had guidelines being developed. Other than the Queen Victoria Hospital, units generally prescribed doses in line with those of the British National Formulary (BNF 2010)\textsuperscript{9}.

\textsuperscript{9} The doses recommended in the BNF are generally standard doses, may not be suitable for patients in whom drugs have altered pharmacokinetics.
Figure 2.1 Antibiotic usage in UK burns centres in 2001 and 2009

The figure shows the percentage of burns units that stated they used the antibiotics listed, at least occasionally. The survey was first undertaken in 2001 and then repeated in 2009.
Aminoglycoside use was consistently high. In 2009, all but one centre used gentamicin (79% in 2001), and eight (62%) also used amikacin (21% in 2001), although generally less frequently (Figure 2.2). Gentamicin was used as empiric therapy by half of the units, whereas amikacin was reserved to treat susceptible organisms on the advice of the microbiologist. Most units administered the aminoglycoside in an extended or “once-daily” dosing schedule (Figure 2.3).

![Figure 2.2. Frequency of use of aminoglycosides by number of units (2009).](image)

Twelve of the thirteen centres used gentamicin in 2009, and eight used amikacin. The frequency of use within the centres was also greater for gentamicin.

![Figure 2.3 Once-daily vs multiple daily dosing of aminoglycosides in 2009](image)

Of the centres who answered the question on administration of aminoglycosides, nine out of the ten centres administered gentamicin, and four out of six administered amikacin as once-daily or extended dose administration.
For all units it had been long-term practice to monitor serum concentrations of the aminoglycosides.

In 2009, all units used glycopeptides, more commonly, vancomycin (Figure 2.4). Vancomycin was used equally as empiric therapy and for the treatment as susceptible organisms, whereas teicoplanin was used only as empiric therapy by one unit. In two cases, teicoplanin was used in higher doses than usually recommended (e.g. in the BNF), and serum concentrations were sometimes or always monitored by three units. With vancomycin, the standard dose was used only in two sites, but all units monitored serum concentrations as a long-term practice. Five units stated that they administered vancomycin as a continuous infusion, and four as an intermittent infusion.

![Figure 2.4. Frequency of use of glycopeptides by number of units (2009)](image)

In 2009, eleven of the thirteen centres used vancomycin at least occasionally, whereas teicoplanin was only used by seven of the centres (at least very rarely).

Many antimicrobials where there were little or no pharmacokinetic data in patients with major burns were being prescribed in 2001. Those that were generally reserved for the treatment of infections in critically ill patients were
cefotaxime, ceftriaxone, chloramphenicol, colistin, imipenem, linezolid, meropenem and Synercid®. The ones in use at the base study site were colistin, imipenem, linezolid and meropenem (Figure 2.5).

As stated previously, the use of meropenem increased from being in seven to thirteen of the centres between 2001 and 2009. In 2009, its frequency of use varied from “occasionally” to “almost certainly”. It was used both as empiric therapy and when susceptible organisms had been identified. Ten of the thirteen units used it on the advice of the microbiologist. Most commonly it was the microbiologist who advised on the dose to use, although four units used local guidelines, and three were advised by the pharmacist. The doses used were generally 1g eight hourly, although one unit sometimes used 2g eight hourly. Other than the study at the Queen Victoria Hospital (the study site), no units monitored serum concentrations.

![Figure 2.5. Frequency of use of meropenem, linezolid, colistin and imipenem by number of units (2009).](image)

The use of linezolid increased from two to ten centres over the seven-year period. Seven units used it “very rarely” and three “occasionally”. In most cases
it was used on the advice of the microbiologist for organisms identified to be susceptible to linezolid, such as MRSA and vancomycin-resistant *enterococci*. The microbiologist or pharmacist generally advised on the dose, which was the standard 600mg every twelve hours. Other than the base site at the Queen Victoria Hospital, no units monitored serum concentrations.

In 2001, only the base study site was using colistin. By 2009, it was used by six units, one of which administered it only by nebuliser (inhaled). Three more used it both nebulised and intravenously. The frequency of use varied between the units from “very rarely” to “almost certainly”. The unit which used it most frequently used it as empiric therapy, whereas the other units used it only for sensitive organisms on the advice of the microbiologist. Doses used were all in line with the standard dose, and were determined by the surgeon, anaesthetist, microbiologist, pharmacist or by using local guidelines. When colistin was being used intravenously, centres either sometimes or always monitored the patients’ serum concentrations. Two units had started doing this in the previous twelve months, whereas for the other two it was long-term practice.

In 2001 imipenem was being used by eight centres. This had dropped to only two centres seven years later, and it was no longer used at the study site. For the two units which used it in 2009, one used it very rarely and one occasionally. Both units used it only on the advice of the microbiologist and one used it as empiric therapy. Doses used were standard doses, and neither unit monitored patients’ serum concentrations.

### 2.4. Discussion

This survey indicates a wide variation in the use of antimicrobials across UK burns units both in 2001 and 2009.

The 2001 survey helped identify four antibacterial agents that could be candidates for a clinical study, measuring serum concentrations in order to calculate pharmacokinetic parameters and make dose recommendations.
Of the four, only imipenem had some published pharmacokinetic data for patients with major burns (Boucher et al. 1990; Dailly et al. 2003a). As discussed in Chapter 1, Section 1.8.3.3, both groups of authors concluded that creatinine clearance was likely to be the major factor in determining dosage requirements, but no dose recommendations were made. Because of the relatively large number of units using imipenem in 2001, this antibiotic was identified as one that required further investigation, despite only occasional use at the study site. However, whilst it was included in the protocol for the clinical study (see Chapter 3), no patients were recruited for imipenem, and it can be seen that by 2009, its use nationally was very low.

The other carbapenem in use was meropenem. In 2001, there were seven units using it, and it was one of the first-line treatments for empiric therapy of life-threatening infections in patients with burns at the Queen Victoria Hospital. There were no pharmacokinetic data published for severely burned patients, and therefore the antibiotic was selected as another for the clinical study.

Linezolid and colistin were both used rarely. However, these antibiotics were used at the base study site, and were generally reserved for the treatment of multi-drug resistant organisms. No pharmacokinetic data of these drugs in severely burned were published for either antibiotic. Sub-therapeutic dosing of these two antibiotics could result in the development of resistance, potentially leaving organisms that were not susceptible to any antimicrobial therapy. Therefore, despite their low usage, they were identified for the clinical study. By 2009, many more units had started using both linezolid and colistin, indicating an increase in multi-drug resistant organisms.

The three antimicrobials identified for the clinical study were therefore imipenem, meropenem, linezolid and colistin. The methodology for this study is described in Chapter 3. Chapters 4 (meropenem), 5 (linezolid) and 6 (colistin) describe each of the three antimicrobials where patient data was collected from the clinical study.
The 2009 survey identified differing practices for other antimicrobials where
dose recommendations for patients with burns have been published. For
vancomycin, two methods for dose calculation have been proposed for
administration by continuous infusion in severely burned patients (Conil et al.
1994; Dailly et al. 2008), but their use in practice has not been ascertained.
This is therefore examined further in Chapter 8.

For gentamicin, most centres in 2009 used extended interval administration
(also known as “once-daily”). However, dose recommendations for severely
burned patients have been made only for multiple dose administration (Zaske et
al. 1991) and it has been suggested that extended-interval dosing may not be
appropriate for many patients with burn injury (Hoey et al. 1997). For this
reason, gentamicin is examined further in Chapter 7.

There are two main limitations to the interpretation of the survey responses.
Firstly, the 2001 survey included burns centres which did not treat intensive
care burns. Therefore it may be that some of the percentages of antibiotic use
would have been higher if the survey had included only centres where intensive
care patients with burns were treated. Secondly, some of the questions were
subjective, particularly those relating to the frequency of usage. However, the
survey appeared to be sufficient to aid with the identification of antibacterial
agents for further study.

2.5. Summary and Conclusions

This survey indicates that there is a wide variation in antimicrobial use in burns
centres in the UK. Four antibacterial agents – imipenem, meropenem, linezolid
and colistin – were identified for a clinical pharmacokinetic study to develop
dosage guidelines. However imipenem was later excluded from the study due
to a decline in its use clinically. Additionally further work is required to
determine the most appropriate dosing schedule of vancomycin, and also to
review the administration of gentamicin and other aminoglycosides in patients
with major burns.
Chapter 3 Methodology of the clinical pharmacokinetic study

3.1. Introduction

The aims of the clinical pharmacokinetic study are to investigate the pharmacokinetic parameters of three antibiotics when administered to patients with major burns, and to produce dosing guidelines for the use of these antibiotics.

The objectives are:

- to measure the serum concentrations of meropenem, colistin and linezolid in adults with major burns (>15% total body surface area) receiving these antibiotics for treatment of severe infections.
- to compare the serum concentrations with those required to treat likely infections.
- to calculate pharmacokinetic parameters such as volume of distribution, clearance and elimination half-life.
- to compare pharmacokinetic parameters calculated in this study of burns patients with other populations.
- to investigate the influence of patient factors on the serum concentrations and pharmacokinetic parameters.
- to produce dosage guidelines for the use of these antibiotics in adults with major burns.
- to ascertain, using the data generated by the study and that previously published, whether there is a model for the dosing of all antibiotics in burns patients.

A clinical study was therefore set up. The base site was the Burns Centre at the Queen Victoria Hospital in East Grinstead.
3.2. Patient recruitment

The aim was to recruit twelve patients for each antibiotic (see statistics in Section 3.12.3). As most burns centres have only one or two intensive care patients at a time, in order to recruit sufficient numbers of patients, it was decided that the study should be multi-centred. Three other centres expressed an interest in taking part, and two reached the stage of approval by the relevant bodies. However, no patients were recruited from the other centres (see section 3.15). Additionally, as previously stated in Chapter 2, Section 2.4 it was initially intended that imipenem would be one of the study antibiotics, but this was not required during the study period, leaving three antibiotics to be studied; meropenem, linezolid and colistin.

3.3. Study population

Patients were included in the study if they had a total body surface area (TBSA) burn of greater than 15% and were receiving any of the antibiotics to be studied which had been commenced according to clinical need. Patients were identified by the consultant microbiologist when advising the medical team on the choice of therapy and the agreement of the patient’s burns surgeon was obtained for the inclusion in the study.

Patients were excluded if they were under the age of sixteen years. This was both because the pharmacokinetics in children may have been different from adults, and also because of the additional ethical requirements relating to issues of consent. Additionally patients were excluded if they were pregnant or breastfeeding, again due to the possibility of altered pharmacokinetics. Patients with known or suspected blood-borne viruses were also excluded.

3.4. Initial drug administration and dosing

The study antibiotics were initially administered at the dose decided by the patients’ clinicians. These were based on the dosage guidelines produced by the researcher in the role of clinical pharmacist (Appendix 3) and were generally the highest dose levels recommended in the summaries of product
characteristics produced by the manufacturers (AstraZeneca 2001a; MSD 2001; Pharmacia&Upjohn 2001a; Pharmax 2001a).

3.5. Assay methods

Blood samples were to be collected and analysed immediately, rather than freezing them and analysing them together at a later date. This enabled the patient receiving the antibiotic to have a dose change if concentrations were low. Two further potential benefits of this were firstly, that when asking for consent, the direct benefit of the study to the patients themselves would be clear, and secondly it was hoped that it would increase the interest of other centres to take part. The Regional Antimicrobial Assay Laboratory at Southmead Hospital in Bristol agreed to analyse the samples which ensured that there would be consistency in the results and no delay in the process. For practical and financial reasons, samples were collected only from Monday to Thursday so that they were both collected and analysed on weekdays.

3.6. Meropenem

The assay of meropenem used by Southmead Hospital was by a high-performance liquid chromatography (HPLC) method published by Lovering et al (1995). In brief, this method used a Hypersil 5ODS stationary phase. The mobile phase was composed of 25% methanol, 1% phosphoric acid and 74% water, with the pump flow rate at 1.0ml/min. Detection was by UV absorbance ($\lambda_{max}$ 296nm). Samples were prepared by mixing with an equal volume of acetonitrile and centrifuged at 5000g for three minutes. 10 microlitres of the supernatant were then injected onto the column.

High performance liquid chromatography is a form of chromatography, where a liquid mobile phase is forced though a stationary phase which is fixed on a column. Substances that are not strongly retained by the stationary phase move quickly away with the liquid phases and are then detected (e.g. by UV absorbance) at a time which corresponds to that substance. Substances that are strongly retained by the stationary phase take longer and the peak will be detected later. The area of the peak correlates with the concentration of the
substance. An example of a chromatogram for meropenem in serum as part of the work undertaken by the researcher as described below and Appendix 4 is shown in Figure 3.1.

![Chromatogram Image]

**Figure 3.1 Example of chromatogram from HPLC of meropenem in serum**

HPLC (high performance liquid chromatography) peaks identify different substances detected. Previous work with meropenem in water identifies that the peak that appears about 5 minutes is meropenem. The numbers at the bottom of the figure show areas of each peak, which correlate with concentrations of the substances. The correlation for meropenem can be been determined by injecting differing concentrations of meropenem in water onto the column and noting the peak areas.

As the samples were to be couriered overnight before analysis, it was necessary to ensure minimal degradation of the samples being sent. One study (Elkhaili et al. 1996) determined that meropenem was stable in serum at 4°C for
24 hours. Another (Robatel et al. 2002) found that there was less than 5% degradation of meropenem in whole blood that was stored for 1.5 hours at 4°C. For practical purposes it would be preferable to send samples for analysis in whole blood rather than serum. Therefore for the current study, experiments were undertaken to determine the stability of meropenem (Appendix 4). This showed that after 24 hours at 4°C, there was more than 5% degradation in whole blood. The stability of meropenem was then determined in serum, which confirmed that there was less than 5% degradation after 24 hours.

### 3.7. Linezolid

The assay of linezolid used by Southmead Hospital was an HPLC method published by Tobin et al (2001). In brief, this method used a Hypersil 5ODS stationary phase, and a mobile phase of 1% ortho-phosphoric acid, 30% methanol and 2g/L heptane sulphonic acid with the pH adjusted to 5 by the addition of 10M sodium hydroxide. The pump flow rate was 1.0ml/min and detection was by UV absorbance (λ<sub>max</sub> 254nm). Samples were prepared by mixing with an equal volume of acetonitrile. These were left to rest for ten minutes at room temperature, before centrifuging at 5000g for five minutes. 20 microlitres of the supernatant were then injected onto the column.

The paper by Tobin et al also confirmed that linezolid was stable in serum at room temperature and 4°C for at least seven days. As it had been found that samples of meropenem would need to be spun down at the study site, it was felt unnecessary to determine the stability of linezolid in whole blood.

### 3.8. Colistin

Serum concentrations of colistin have traditionally been measured by using the agar plate diffusion method with *Bordetella bronchiseptica* 4617 as the test organism, a modification of the U.S. Food and Drug Administration method for the assay of polymyxin (Boger and Gavin 1962; Leroy et al. 1989). This method is unable to distinguish between the colistin sulphomethate and its active metabolite colistin (Barnett, Bushby and Wilkinson 1964) and is discussed further in Chapter 6. The microbiological assay also lacks specificity,
particularly when samples contain other antibiotics that are active against the test strain. More recently methods for HPLC analysis have been published (Le Brun, De Graaf and Vinks 2000; Reed et al. 2001; Li et al. 2002; Li et al. 2003b), but only the methods by Li et al (2002 and 2003) distinguished between the two forms of colistin.

The method used by the Southmead Laboratory (Wootton, Holt and MacGowan 2005) was a bioassay, but had *E.coli* as the indicator organism. In this assay, which had been used for the previous three years, an inoculum containing the *E.coli* indicator strain was applied to an agar plate. An aqueous stock solution of colistin sulphomethate was prepared, and then diluted, using human serum, to concentrations ranging from 0.5 to 128mg/L. Each concentration was placed with a positive meniscus in triplicate in 10mm wells cut into the agar. After being left at room temperature for four hours, the plates were then incubated at 37°C for 24 hours. For each well, the zone of inhibition was measured and the mean of the diameters for each concentration was plotted against log of the concentration in order to produce a standard curve. This method was stated to be more accurate and more sensitive than the microbiological method using *B.bronchiseptica* and to be less complex than HPLC methods.

Because of the limitations of the microbiological assay, it was decided to try to replicate the published HPLC methods published that could distinguish between the forms of colistin. If this was possible, the serum samples could be split, with half going to Southmead for immediate analysis. The other half would be analysed by the HPLC. This would have enabled the microbiological method to be compared with the newer method, and allow the pharmacokinetics of both colistin and colistin sulphomethate to be calculated. However, the HPLC method was unable to be replicated (Appendix 5), and only the microbiological assay was used for the pharmacokinetic study.

The Southmead laboratory advises that samples may be sent by post (Antimicrobial_Reference_Laboratory 2007), although a literature search using Embase® and Medline® up to 2002 revealed no stability data for colistin sulphomethate in serum at either room temperature or 4°C. During the time
when the pharmacokinetic study was being set up and laboratory work was being undertaken, Li et al (2003b) established that there was no detectable degradation of colistin sulphomethate in water after 48 hours at 4°C. At 37°C, in plasma, more than 60% of colistin sulphomethate was hydrolysed to colistin after 24 hours. In 2005 data published from Southmead Hospital (Wootton, Holt and MacGowan 2005) confirmed the stability of colistin sulphomethate in serum, with less than 10% change over 7 days at 4°C.

More is discussed regarding methods of analysis for colistin and the relevance to this study in Chapter 6.

3.9. Sample collection and handling

A set of blood samples were collected over one dose interval at least 24 hours after antimicrobial therapy had commenced. This allowed time for the antibiotics to reach steady-state\textsuperscript{10}, and for patient information and consent to be given (Section 3.13.2). Samples were taken immediately before a dose, 30 minutes after the start of the administration of the dose\textsuperscript{11}, then at one, two and four hours, and immediately before the next dose (or at eight hours in the case of linezolid which had a twelve-hourly dosing regimen).

Blood samples (approximately 3ml) were collected in serum gel tubes by nursing staff. To aid them with this, a template sheet was prepared (Appendix 6), which could be completed to remind them of the times of sampling, and for them to record the exact times that the dose was given and samples were taken.

Samples were spun down immediately after collection (Appendix 7) in order to separate the serum from blood cells, platelets and clotting factors, and the serum layer transferred to an eppendorf. These were then labelled and stored at 4°C. When all the samples had been collected, they were packaged in a cool

\textsuperscript{10} Steady-state is achieved when the rate of input is equal to the rate of elimination. In practical terms this is achieved after four to five half-lives. This is described further in Chapter 4 Section 4.1.5.1.

\textsuperscript{11} Depending on the antibiotic administration time usually ranged for 5 to 30 minutes
box, and sent by overnight courier to Southmead Hospital. Results were faxed to the study site the following day.

Pharmacists and pharmacy technicians were trained to centrifuge the samples, remove the serum layer, and package the samples ready for the courier. This required the writing of several standard operating procedures and a record of competency (Appendix 7). Additionally Pharmacy staff members were required to familiarise themselves with Trust policies relating to needlestick injuries and blood spillage.

3.10. Initial analysis, dose adjustment and resampling

Serum concentrations were plotted on a graph of concentration versus time and a visual estimate was made as to whether the dose the patient was receiving was therapeutic. (See Chapters for 4, 5 and 6 for the measure of efficacy selected for each antibiotic.) If they were thought not to be so, doses were increased, as advised by the clinical pharmacist.

If possible a further set of samples were collected at least 24 hours after any dose change, but this depended on the length of the antibiotic course. Resampling also took place if there was a significant change in the patient’s renal function.

3.11. Data collection

To enable analysis of data, a patient data sheet was prepared. This was amended after two patients to enable easier access to information (Appendix 8). The information on the sheet included:

1. Patient Demographics
   - Age and gender
   - Weight

2. Burn Details
   - Burn total body surface area
• Full and partial thickness burn surface area
• Presence of inhalation injury
• Percentage burn remaining at time of diagnosis of infection

3. Details of infection
• Date infection diagnosed
• Site of infection the antibiotic is being used to treat if known and date
• Any identified pathogens and date
• Susceptibilities of organisms to antimicrobial agents (on or close to day of starting antibiotics)

4. Antibiotic details
• Dose
• Frequency
• Length of Course

5. Routine laboratory investigations
• Serum creatinine and creatinine clearance
• Serum albumin

6. Other
• Post-burn day when blood taken

7. Patient outcome
• length of stay in ITU
• survival / mortality.

Whilst there were insufficient patient numbers for this study to determine any differences in survival, this data would give an indication of survival compared with that in the literature.
3.12. Pharmacokinetic analysis

3.12.1. Calculation of pharmacokinetic parameters

Data was analysed using WinNonlin®. The following parameters were calculated based on a non-compartmental model: Volume of distribution (Vd), half-life (t½), clearance (CL), area under the concentration versus time curve from time zero to infinity (AUC0-∞) and peak serum concentration (Cmax). (Pharmacokinetic analysis from first principles is undertaken for Chapters 7 and 8).

3.12.2. Predicted effect of different dose schedules

For each patient, the percentage of the dose interval above the minimum inhibitory concentration (T>MIC) and serum concentrations were predicted for different dosing schedules. Individual patient parameters were used, rather than the mean, as large inter-patient variation was likely. The values predicted were based on the pharmacokinetic parameters calculated from the first set of samples taken. The formulae used are shown in Appendix 9.

3.12.3. Statistics

The sample size calculation of twelve patients was based on detecting clinically significant differences in the pharmacokinetic parameters, clearance (CL) and volume of distribution (Vd). Variations in these parameters directly affect the dose required. Based on available data, a best guess was made at what differences are required for them to be of significance in clinical practice. Using Minitab 15 (2006 Minitab Inc) the number of patients needed for each antibiotic to show an effect size (or standardised difference) of 1 was calculated, i.e. to detect a difference of one standard deviation from the mean. This is calculated by dividing the expected difference between the mean in healthy volunteers and the mean in burns patients by the standard deviation. All of the study antibiotics in healthy volunteers have a published SD of 30% or less as a proportion of the

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12 A non-compartment model was used as the intervals between sampling was unlikely to allow accurate calculation of parameters in the distribution phase. In a non-compartment model, calculation of parameters is based on the total drug exposure which is estimated by the area under the concentration-time curve.
mean. This is the likely difference that would be necessary to need to make a
dose adjustment. For example, meropenem has a mean clearance of
155.8ml/min with a standard deviation of 40.6. Therefore if the mean in burns
patients was found to be below 115.2 or above 196.0ml/min, the best guess is
that the difference would be clinically relevant.

A sample size of 12 patients per antibiotic was therefore selected. With this
number of patients, a single group t-test with a 0.05 two-sided significance level
would have 80% power to detect an effect size of 0.889 (i.e. slightly less than 1
standard deviation).

This sample size may seem to be small, but large differences in the
pharmacokinetic parameters in burns patients compared with the values
reported in healthy volunteers were expected. The sample size was similar to
numbers in other antibiotic pharmacokinetic studies, such as with ciprofloxacin
(Garrelts et al. 1996) and piperacillin-tazobactam (Bourget et al. 1996) which
have led to dosage guidelines being adopted in clinical practice.

Pharmacokinetic parameters in this study were compared with both single
studies (e.g. one other burns study) and multiple studies of the same population
(e.g. healthy volunteers). Where there was a comparison with one study only,
the student’s t-test was applied. Where the comparison was with a group of
studies (e.g. healthy volunteers), one-way analysis of variance was used to
determine whether there was a significant difference between any of the
studies. To ascertain whether there was a significant difference (P < 0.05)
between this study and each individual study, one-way analysis of variance,
using Duncan’s multiple range test (a recognised statistical method) was
applied.

When investigating the influence of patient factors, the student’s t-test was
applied to determine any differences in both patient and pharmacokinetic values
between those who had therapeutic serum concentrations at standard
recommended doses and those who required more frequent dosing. One way
analysis of variance was used to measure the correlation between
pharmacokinetic parameters and patient factors. Pearson’s product moment correlation coefficient was applied to determine the extent of the linear relationship.

3.13. Legislative Requirements

For a study of patients to take place, it must show itself to be able to produce high quality data to the International Conference on Harmonisation – Good Clinical Practice (ICH-GCP) standards. The EU Directive 2001/20/EC, article 1, clause 2 defines GCP: “Good clinical practice is a set of internationally recognised ethical and scientific quality requirements which must be observed for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects” (European Parliament 2001). At the time of the start of the study, the EU directive had not yet become law in the UK, but later became so. The aims of the Directive were to provide a consistent approach to clinical research across Europe, to establish clear procedures and to provide an environment for conducting clinical research that protected patients, without hampering the discovery of new medicines. Whilst this study of burns patients does not have the aim of discovering a new medicine, the standards set out in the directive still apply. Briefly these include:

- Appropriate training and experience for the investigator
- Compliance with the protocol
- Ethical approval, particularly relating to information and patients and consent
- If the research is classed as a clinical trial, approval from the country’s regulatory body. In the UK, this is the Medicines and Healthcare products Regulatory Agency (MHRA).

3.13.1. Trust Research and Development Committee

Once the protocol was written, approval was required by the Trust Research and Development Committee at every site where it is to take place. The protocol was approved by the Queen Victoria Hospital R&D Committee on the 9th October 2002.
3.13.2. Ethical approval

Following approval by the Trust R&D Committee the protocol was submitted to the Ethics Committee. As the study was intended to be multi-centred, an application was made to a Multi-Centre Ethics Committee (MREC). At the time of application, a central office assigned the protocol to next available MREC meeting in the country, and the application for this study was considered by the Northern and Yorkshire Ethics Committee. Once approved by the MREC, a submission was required for approval by the local ethics committee of every site where the study was to take place.

The application to the Northern and Yorkshire MREC was made in April 2003. This included details regarding consent for the study. It was proposed that whenever possible, the patients themselves would be informed of the study, given a patient information leaflet and they would then have 24 hours to consider the study before being asked to sign the consent form. In many cases however, patients would be sedated and ventilated, so not capable of consent. They were therefore classed as incapacitated adults. In such cases, it was proposed that the patient’s next-of-kin was asked – after appropriate information was given and 24 hours had elapsed – whether it was their opinion that the patient would consent to the study if they were able to do so. Blood samples could then be taken, but retrospective consent to use the data was obtained from any patients who were later able to give it.

This application was approved subject to amendment. There were eleven points that required a response, which included amendments to the protocol, and the patient information leaflets. These were addressed (Appendices 10 and 11), and the study was given a favourable opinion in July 2003. Local research ethics committee approval for the study to take place at the Queen Victoria Hospital was received in March 2004.

It is a requirement that the ethics committee receive an annual update of the progress with the study. In addition to these there were two substantial amendments submitted:
• In 2005. During the study it became clear that some sedated patients who therefore required consent from their next-of-kin, did not always have a known next-of-kin, or that they were not contactable. These patients could not be recruited to the study, and were therefore not able to have serum samples measured and doses adjusted if necessary. A substantial amendment was submitted for a doctor looking after the patient, but not involved with the study (consultant anaesthetist) to act as the patient’s legal representative. This was in line with the current recommendations relating to vulnerable adults. However the amendment did not receive a favourable opinion for reasons such as the Committee were not convinced that the unavailability of a next-of-kin was likely to have a significant effect on recruitment. Whilst there was an option to resubmit a modification to the amendment, it was decided not to pursue this, due to time limitations and doubts as to whether a resubmission would be successful.

• In 2008. An interim analysis of data on meropenem showed that a dose increase was required in some patients. It was therefore considered that it would be unethical not to measure serum samples in all major burns patients, and this should become part of routine clinical practice, rather than a study, at least until dosage recommendations could be made. The substantial amendment proposed that only antibiotics where more serum samples were taken than could be clinically justified should remain as a research study. This would mean that meropenem and linezolid would no longer be part of the study. With these antibiotics, several samples over the dose interval were required to determine marker of efficacy and would additionally allow pharmacokinetic analysis. The only antibiotic to remain in the study would be colistin, as its efficacy was thought to be related to its peak serum concentration, and therefore it could not be clinically justified to take additional samples to calculate pharmacokinetic parameters. Initially the Committee could not give a favourable opinion, but after modification of the substantial amendment, the principle proposed above was approved. However, the Committee was unable to give a favourable opinion to the amendment because of the changes to the consent forms made as part of the submission. As a substantial amendment can only be modified once, a
new substantial amendment was submitted. This received a favourable ethical opinion early in 2009.

In late 2009, it was decided that as colistin had not been required at the Queen Victoria Hospital for a few years, the study should be closed. Therefore forms were completed for the MREC and MHRA to inform them of this. A report of the findings was to be submitted to the MREC within one year of notification of the end of the study (November 2010).

3.13.3. **Medicines and Healthcare products Regulatory Agency (MHRA)**

When work on the study set-up was first commenced in 2002, there was uncertainty as to whether the study was classed as a clinical trial. This was discussed with the Medicines Control Agency (MCA), and the advice was given that it was not a clinical trial. This meant that authorisation of a clinical trial by the MCA was not required. In 2005, when a new centre was due to commence the study, the R&D Committee at that site viewed it as a clinical trial. The Medicines and Healthcare products Regulatory Agency (MHRA, previously the MCA) were contacted. This time, under revised definitions, it was classed as a clinical trial. This resulted in the suspension of the study until Clinical Trial Authorisation was granted. To achieve this, the study had to be registered with the European Clinical Trial Database, and a submission made to the MHRA. Additionally the study now required a “sponsor” to take responsibility for the initiation, management and / or financing of clinical trial. The Queen Victoria Hospital agreed to become the sponsor, with a legal agreement was drawn up. The study was then able to receive clinical trial approval from the MHRA.

3.14. **Promotion of the study and informing / training staff**

As this was a clinical study on patients, the participation of medical, nursing and pharmacy staff was required. The study was promoted by several presentations to nursing and pharmacy staff, and at the Trust Multidisciplinary Research and Development meeting. As each patient was recruited, the study was explained again to nursing staff looking after the patient at the time. To aid staff with the whole process, a checklist was written (Appendix 12).
3.15. Other centres

Two other centres agreed to participate in the study, but neither recruited any patients.

The first centre was included with the original application and ethical approval was received in 2003. However the Trust R&D Committee had some difficulties with the protocol, including the fact that it was not at the time classed as a clinical trial, and approval was not received until 2007. Following this a presentation was given to medical, nursing and pharmacy staff at the site, but no patients were recruited to the study, due to lack of dedicated staff time.

The second centre became involved in 2005. A presentation was given to medical staff, and applications made to the Trust R&D Committee and the local ethics committee. Since the commencement of the study, the process for these applications had become more centralised and electronic. Resubmission of the original information made to the MREC which had been completed on paper was therefore undertaken. After the appropriate approvals had been given, the consultant named as the principal investigator left the Trust.
Chapter 4 Meropenem

4.1. Introduction

Meropenem is a carbapenem antibiotic possessing a very broad spectrum of activity, so is generally reserved to treat infections in severely ill patients. It is most commonly used against multi-resistant bacteria or for empiric treatment of sepsis.

Carbapenems all possess a beta-lactam ring as part of their structure, as do penicillins and cephalosporins. Carbapenems differ from other beta-lactams as they have a carbon atom at position 1 of the bicyclic ring and a double bond between positions 2 and 3 (Yang, Bhachech and Bush 1995). Additionally they have a hydroxyethyl side chain that is different from most penicillins and cephalosporins which have an acylamino substituent on the beta-lactam ring (Mouton 2000). The chemical structure of meropenem (Figure 4.1) differs from other carbapenems by having a dimethylcarbamoypyrrolidinethio side-chain attached to the C-2 (Moellering Jr, Eliopoulos and Sentochnik 1989).

4.1.1. Mode of action and resistance of meropenem

All beta-lactam antibiotics exert their action by blocking the final stage of bacterial cell-wall synthesis. Their main effect is thought to be the inhibition of transpeptidases, which enables cross-linking of peptidoglycan layers. Cross-linked peptidoglycan layers are needed to give the cells their structural integrity (Chambers 2005a). Transpeptidation is catalysed by high molecular weight (> 50kD) penicillin-binding proteins (PBP). Beta-lactam antibiotics inhibit PBP through covalent binding of the active site serine residue.
Meropenem is a carbapenem antibiotic. Carbapenems differ from other beta-lactams as they have a carbon atom at position 1 of the bicyclic ring, a double bond between positions 2 and 3 and a hydroxyethyl side chain that is different from most penicillins and cephalosporins. The chemical structure of meropenem differs from other carbapenems by having a dimethylcarbamoypyrrolidinethio side-chain attached to the C2.

There are thought to be two main reasons why carbapenems have such a broad spectrum of activity. Firstly they have increased stability to beta-lactamases, compared with other beta-lactams due to the unusual trans-conformation of the hydroxyethyl side-chain (Mouton 2000). Secondly they are able to traverse through the outer lipopolysaccharide layer of Gram-negative bacteria through a specific outer membrane protein, OrpD, (and possibly other proteins for meropenem) rather than OmpC or OmpF which are used by penicillins and cephalosporins (Chambers 2005b).
Carbapenems bind with high affinity to most high molecular weight penicillin binding proteins of Gram-positive and Gram-negative bacteria, although there are differences in their affinity to the different PBPs. In Gram-negative organisms, meropenem binds primarily to PBP2 and PBP3, whereas another carbapenem, imipenem, primarily binds to PBP1 and PBP2. This may explain why meropenem has better activity against Gram-negative organisms (Mouton 2000). Meropenem's dimethylcarbamoylpyrrolidinethio side-chain is thought to further increase its spectrum of activity, particularly against *Pseudomonas* spp. (Moellering Jr, Eliopoulos and Sentochnik 1989).

Bacteria may become resistant to carbapenems by four mechanisms:

1. production of low affinity PBP targets
2. diminished permeability, often due to the absence of OrpD (in Gram-negative bacteria, usually in conjunction with the production of beta-lactamase)
3. efflux of drug across the outer membrane in Gram-negative bacteria
4. production of a beta-lactamase that will hydrolyse carbapenems

Two common burns pathogens are intrinsically resistant to meropenem. Resistance to *Stenotrophomonas maltophilia* is due to hydrolysis by Ambler class B enzymes (zinc-dependent metalloenzymes) produced by these organisms, whereas with *Enterococcus faecium*, resistance is due to the production of low affinity penicillin-binding proteins (Chambers 2005b).

**4.1.2. Indications of meropenem**

In the UK, meropenem is licensed in adults and children over 3 months of age for the treatment of pneumonia, broncho-pulmonary infections in cystic fibrosis, complicated urinary tract infections, complicated intra-abdominal infections, intra- and post-partum infections, complicated skin and soft tissue infections and acute bacterial meningitis. Meropenem may also be used in the management of
neutropenic patients with fever that is suspected to be due to a bacterial infection (AstraZeneca 2010).

4.1.3. Dose and administration of meropenem

Meropenem is licensed for administration by either intravenous bolus over 5 minutes or intermittent infusion over 15 to 30 minutes.

The usual adult dose is 500mg to 1g every eight hours depending on the severity of infection. A dose of up to 2 g three times daily in adults and adolescents may be required for the treatment of some types of infections, such as nosocomial infections due to *Pseudomonas aeruginosa* or *Acinetobacter* spp. Dose adjustments are not thought to be required for patients with hepatic impairment, but should be reduced in renal impairment (AstraZeneca 2010).

4.1.4. Toxicity of meropenem

Meropenem is generally well tolerated. Animal studies have shown meropenem to be nephrotoxic only at high doses (>500mg/kg). For an IV dose the LD$_{50}$ (the dose required to kill 50% of the study animals) in rodents is greater than 2000mg/kg. In repeat dose studies (up to six months) in dogs with doses of 500mg/kg only minor effects were seen, including a small decrease in red cell parameters and an increase in liver weight. A dose of 1g in a human is approximately 10 to 20mg/kg, which is well below the toxic doses reported in animals. No specific treatment is recommended for overdose, except for patients with renal impairment where haemodialysis may be required (AstraZeneca 2001b).
4.1.5. Pharmacokinetics of meropenem

4.1.5.1. Pharmacokinetics of meropenem in healthy subjects

Meropenem is not orally absorbed and is negligibly (approx 2%) protein-bound (Drusano and Hutchison 1995). Distribution is primarily extra-cellular, with concentrations in the tissues being in the same range as in plasma (Wise et al. 1990; Mouton and Michel 1991). Penetration of the drug into cerebrospinal fluid is about 20%, with wide individual variations (Dagan et al. 1994).

A five minute bolus in healthy volunteers results in peak plasma levels of 52mg/L for a 500mg dose and 112mg/L for a 1g dose (AstraZeneca 2001b). The most common dose schedule used in clinical trials was 1g every eight hours. With this dose at steady-state, trough levels were approximately 0.25mg/L in normal volunteers with normal renal function (Drusano and Hutchison 1995). As described in Chapter 3 Section 3.9, steady-state is achieved when the rate of input is equal to the rate of elimination. Steady-state for administration of a drug by continuous infusion is illustrated in Figure 4.2 and for an intermittent bolus dose in Figure 4.3.
Figure 4.2 Illustration of steady-state for a continuous intravenous infusion

A drug is infused intravenously at a constant rate (e.g. mg/hour). The serum concentration will increase more gradually over time, until the rate of input is the same as the rate of elimination (approximately four half-lives). In this figure steady-state concentration ($C_{ss}$) is 4.5mg/L and is reached at approximately 6 hours.

Figure 4.3 Illustration of steady-state for an intravenous bolus regimen

In this example, the same dose of a drug is given every four hours. It has an elimination half-life of about 4 hours. When steady-state is reached after about 16
hours, the peak serum concentration at steady-state ($C_{\text{ss max}}$) is 4mg/L and the trough concentration ($C_{\text{ss min}}$) is 2mg/L.

Jones et al (1997) compared the pharmacokinetics of meropenem after intravenous administration of 1g over 2, 3, and 5 minutes. In patients dosed over 2 minutes and 3 minutes, the highest observed plasma concentrations occurred between 1 and 5 minutes after the end of the injection. Bax et al (1989) measured lower peak serum concentrations following a 30 minute infusion, but other parameters such as volume of distribution, half-life and clearance were similar to the shorter administration time. Table 4.1 lists the pharmacokinetic parameters of meropenem in healthy subjects.

<table>
<thead>
<tr>
<th>Administration time</th>
<th>2min</th>
<th>3min</th>
<th>5 min</th>
<th>30 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (mg/L)</td>
<td>110.0 +/- 46.2</td>
<td>90.6 +/- 23.3</td>
<td>93.6 +/- 22.8</td>
<td>55.4 +/- 3.7</td>
</tr>
<tr>
<td>T ½ (h)</td>
<td>0.93 +/- 0.12</td>
<td>0.93 +/- 0.10</td>
<td>0.98 +/- 0.14</td>
<td>0.96 +/- 0.05</td>
</tr>
<tr>
<td>AUC$_{0-\infty}$ (mg.h/L)</td>
<td>65.3 +/- 9.86</td>
<td>67.7 +/- 12.68</td>
<td>68.2 +/- 7.36</td>
<td>66.9 +/- 4.6</td>
</tr>
<tr>
<td>$Cl_p$ (mL/min)</td>
<td>250 +/- 41.0</td>
<td>245 +/- 43</td>
<td>239 +/- 29.3</td>
<td>254 +/- 16</td>
</tr>
<tr>
<td>Vd$_{ss}$ (L)</td>
<td>16.7 +/- 2.96</td>
<td>16.6 +/- 2.69</td>
<td>16.6 +/- 2.58</td>
<td>17.8 +/- 0.7</td>
</tr>
</tbody>
</table>

Table 4.1 Derived pharmacokinetic parameters for meropenem in healthy subjects (mean +/- SD)

Data extracted from Bax et al. (1989) and Jones et al. (1997). The table shows that, following a 1g dose, whilst $C_{\text{max}}$ (maximum concentration measured) appears to decrease as time over which the drug is administered increases, there were little differences in T½ (elimination half-life), AUC$_{0-\infty}$ (area under the concentration-time curve extrapolated to infinity), $Cl_p$ (plasma clearance) and Vd$_{ss}$ (volume of distribution at steady-state).
Meropenem is mainly eliminated unchanged by the kidney. Only one metabolite has been identified, ICI 213689, which is the open β-lactam ring of meropenem and therefore is inactive (Harrison et al. 1989). The open ring may be formed by the cleavage of the β-lactam bond by chemical hydrolysis or by enzyme action (Thyrum et al. 1997). Meropenem has enhanced resistance to mammalian dehydropeptidases (Moellering, Eliopoulos and Sentochnik 1989; Farthing, Jeffries and Anderson 1999), thereby avoiding the need for co-administration with a renal dehydropeptidase inhibitor, as is the case with imipenem.

The pharmacokinetic profile of meropenem best fits a two-compartment model (i.e. distribution phase then an elimination phase) with clearance best described using a first order kinetics model (i.e. logarithmic decline) (Kelly, Hutchison and Haworth 1995). Renal clearance accounts for the majority of the drug clearance for both meropenem and ICI 213689. It is thought that meropenem undergoes tubular secretion as well as glomerular filtration, as its renal clearance is greater than creatinine clearance (Meyer et al. 1999). Over a period of twelve hours almost 70% of meropenem and 20% of ICI 213689 was recovered from the urine (Harrison et al. 1989). A compilation of meropenem clearance data from several studies shows a linear relationship between creatinine clearance and meropenem clearance (Drusano and Hutchison 1995).

4.1.5.2. Pharmacokinetics of meropenem in patients with severe burns

Yoshida et al (1993b) reported the pharmacokinetics of meropenem in rats seven days post-burn and found that the penetration into full-thickness burned skin was higher than in unburned skin. The peak serum concentration at a dose of 20mg/kg was much lower than would be expected in humans (7mg/L at 15 minutes post-administration) and was only slightly higher than that measured in the fluid exudate,

The first report describing the pharmacokinetics of meropenem in burns patients was also by Yoshida et al (1993a). At a dose of 1g twice a day (approximately
15mg/kg) in five patients, serum concentrations at one hour were approximately 20 – 25mg/L after which the levels decreased rapidly. No data on the burn size, age of patient, renal function or time post-burn is given.

In his review of pharmacokinetics of antibiotics in patients with burns, Weinbren (1999) reports low serum concentrations in one patient, a 13 year-old boy weighing 50kg. At a dose of 1g every eight hours (60mg/kg/day i.e. 1.5 times the standard recommended maximum dose), the serum concentration one hour after administration was 8.8mg/L. Applying data from a study of hospitalised non-burned children (Blumer et al. 1995) the peak at this dose would be expected to be approximately 40mg/L.

4.1.6. Pharmacodynamics of meropenem

Antibiotics generally exhibit either a concentration-dependent or time-dependent killing. Meropenem and other beta-lactams are thought to fall into the latter group, although there is no consensus on exactly what proportion of the dose interval needs to be above the minimum inhibitory concentration (MIC) for maximal efficacy. Additionally there is some evidence that other factors such as the post-antibiotic effect, and peak serum concentrations, may in part determine the efficacy.

Using numerous multiple-dosing regimens (varying doses and frequencies of administration) in a neutropenic mouse thigh infection model, Vogelman et al (1988) showed that the time the serum concentration exceeded the MIC was the most important parameter determining the efficacy of the beta-lactams cefazolin, penicillin G and ticarcillin. By measuring the log cfu/ml after 24 hours of treatment, they noted that the percentage of time above the MIC required to achieve maximum efficacy varied according to the drug-organism combination, with some e.g. cefazolin - Escherichia coli appearing to be 100% whereas others such as cefazolin-Staphylococcus aureus seemed to be around 50%. The

13Colony-forming unit (cfu) is a measure of the number of viable microbial cells.
difference was thought to be due to the post-antibiotic effect, and the authors suggested that the dosing interval for a beta-lactam should be no greater than the time above the MIC plus the duration of the post-antibiotic effect, if there is one. Vogelmann was also one of the authors in a subsequent study (Leggett et al. 1989), this time using a neutropenic mouse model of pneumonitis, as it was considered a better representation of human infection. They used one organism, *Klebsiella pneumoniae*, with the beta-lactams cefazolin, ceftazidime and imipenem. Employing similar methods as the previous study (Vogelman et al. 1988), they again found that the time above the MIC was the best marker of efficacy for this group of antibiotics.

Drusano (1988) proposed that serum concentrations of beta-lactams which continually exceed the MIC of a particular pathogen may improve therapeutic outcome (Drusano 1988). The author suggested that meropenem may be one of the exceptions to this as it has a post-antibiotic effect against Gram-positive and Gram-negative organisms, although the presence of a post-antibiotic effect has been questioned by other researchers. Whilst some have reported the existence of a PAE *in vitro* and *in vivo*, others have found no significant effect. Findings are therefore contradictory and appear to be dependent on the method used to measure the PAE (Fuentes et al. 1995).

Animal studies of other beta-lactams have demonstrated that antibiotic concentrations do not need to constantly exceed the MIC to exert sufficient antimicrobial activity. Studies of amoxicillin and amoxicillin-clavulanate against a large number of strains of *Streptococcus pneumoniae* showed that mortality in neutropenic mice at 4 days was 80 to 100% when serum concentrations were above the MIC for less than 20% of the time, and maximal survival was reached when this figure was 40% (Andes and Craig 1998). In their 1993 conference paper, Craig *et al* reported that there were differences in the time above the MIC for different classes of beta-lactams to produce a bacteriostatic effect and these figures varied according to the organism (Craig, Ebert and Watanabe 1993). They concluded that an effective T>MIC (i.e. percentage of the dose interval where
serum concentrations were above the minimum inhibitory concentration) (mean % of dose interval ± SD) was:

- lowest with the carbapenems, imipenem and biapenem (20±4 to 26±10 depending on dose-interval) and highest with cephalosporins (35±11 to 53±20).
- lower against staphylococci (24±9) than streptococci (41±12) and Gram negative bacilli (26±15)
- lower with the carbapenems, imipenem and biapenem, against Psuedomonas aeruginosa (16±4) than against other Gram negative bacilli (27±5).
- similar in the lung (33±12) and thigh (33±20) models for the strain of Klebsiella pneumoniae studied, although the large standard deviations should be noted.

The T>MIC measured by Craig, Ebert and Watanabe are for a bacteriostatic effect. In Craig’s 1998 review of the rationale for antibacterial dosing, a study of the efficacy of cefotaxime against Klebsiella pneumoniae in the lungs of neutropenic mice is reported. In this review, an in vivo bacteriostatic effect was observed when serum levels were above the MIC for 30 – 40% of the dosing interval, whereas maximal killing was approached when levels were above the MIC for 60 – 70% of the time (Craig 1998). In his review of the pharmacodynamics of antibiotics, Drusano (2003) quoted personal communication with W.A. Craig, and stated that the maximal kill end point for penicillins was T>MIC was 50%, and for carbapenems this figure was 40%.

Results in a study of ceftazidime using an in vitro pharmacokinetic model mimicking human serum drug concentrations (Mouton and Den Hollander 1994) suggested that, in cases such as neutropenic patients, a sustained serum concentration approximately 1 x MIC was insufficient to treat infections caused by Pseudomonas aeruginosa. The authors suggested that a continuous infusion that achieved a concentration of four times the MIC was more likely to achieve maximum efficacy.
Clinic studies of beta-lactam antibiotics in humans also indicate that the time above the minimum inhibitory concentration is a key predictor of clinical outcome. Heffelfinger et al (2000) undertook retrospective reviews of patients with community acquired pneumonia. They found that there was good efficacy with various beta-lactams with penicillin-intermediate and penicillin-resistant *Streptococcus pneumoniae* as long as the predicted serum concentrations of the drug exceeded the MIC for 40 – 50% of the dosing interval.

Tam et al (2002) found that for cefipime, together with an aminoglycoside, in 20 patients with Gram-negative infections (including one patient with a concurrent *Staphylococcus aureus* infection), the microbiological success was associated with T > MIC (89% success when T > MIC was 100%, 0% when less than 100%), but that the strongest relationship to the probability of microbiological success was T>4.3 x MIC. The probability of 80% success was T>4.3 x MIC for 83% of the dosing interval, and for 90% success, this figure was 95% of the dosing interval.

Focussing on studies specific to carbapenems, Bowker et al (1996) measured bacterial kill *in vitro* at different concentrations. They found that meropenem exhibited a concentration-dependent killing against *Escherichia coli* (MIC 0.015mg/L), *P. aeruginosa* (MIC 0.5mg/L) and *S. aureus* (MIC 0.03 to 0.06mg/L) only in concentrations up to 50mg/L. The post-antibiotic effect and the modified controlled effective regrowth time (mCERT, a measure of bactericidal activity and PAE) increased up to 75mg/L. Of note is that there were no concentrations between 5mg/L and 50mg/L for the bacterial kill study, and between 5mg/L and 75mg/L for the PAE and mCERT arm. In clinical practice concentrations between these two values are often recorded, so its relevance to clinical practice is unclear.

Bowker et al (1998) used a pharmacokinetic model to study the pharmacodynamics of meropenem. When the efficacy was assessed by the area under the bacterial time-kill curve (i.e. a plot of log$_{10}$cfu/ml against time), no relationship between MIC and efficacy was noted. However, using a different
method of assessment, an inverse relationship between the change in \( \log_{10} \) cfu/ml and peak concentration to MIC was seen for *E.coli* and *S.aureus*, but not for *P.aeruginosa*. The authors suggest that this may be due to the higher MIC of *P.aeruginosa* (0.5 mg/L vs 0.015mg/L for *E.coli* and 0.06 mg/L for *S.aureus*). The paper states that T>MIC is related to reduction in cfu/ml after 24 hours for *E.coli* and *S.aureus*, but not for *P.aeruginosa*. This conflicts with the figure in the paper which indicates that the reduction is seen for *E.coli* and *P.aeruginosa*, but not for *S.aureus*.

Fuentes *et al* (1995) compared two dosing regimens of meropenem in the neutropenic mouse thigh model. They used the same total daily dose, but gave one regimen at twice the dose and double the dosing interval, compared with the other. They found that the more frequent dosing schedule, where the T>MIC was higher, was more effective for *E.coli*, but there was no differences between the two regimens for *S.aureus*.

Flückiger, Segessenmann and Gerber (1991) simulated the pharmacokinetic profiles of imipenem in the neutropenic mouse thigh infection model and found a greater reduction in log of cfu/thigh as the doses increased (Table 4.2).

<table>
<thead>
<tr>
<th>Simulated dose (mg/kg)</th>
<th><em>P.aeruginosa</em> (MIC 2mg/L)</th>
<th><em>E.coli</em> (MIC 0.25mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>Reduction then increase</td>
<td>Increase</td>
</tr>
<tr>
<td>2.2</td>
<td>Reduction then increase</td>
<td>Increase</td>
</tr>
<tr>
<td>8.8</td>
<td>Reduction then no change</td>
<td>Sustained reduction</td>
</tr>
<tr>
<td>17.5</td>
<td>Reduction then no change</td>
<td>Sustained reduction</td>
</tr>
<tr>
<td>35.0</td>
<td>Sustained reduction at 6 hours</td>
<td>Sustained reduction</td>
</tr>
</tbody>
</table>

*Table 4.2 The effect of imipenem on log of cfu/thigh adapted from Fluckiger, Segessenmann and Gerber (1991)*
Plasma kinetics at each of the doses used indicated that T>MIC needed to be for least 70 to 80% of the treatment period for maximum efficacy. In humans the usual adult total daily dosage of imipenem is 1 – 2 g administered in 3 – 4 equally divided doses. In infections due to less sensitive organisms, the daily dose may be increased to a maximum dose of 1g every six hours. The lowest dose of imipenem is therefore 250mg which is approximately 4mg/kg, whereas a dose of 1g is approximately 14mg/kg.

Walker et al (1994) also used the neutropenic mouse model to quantify the influence of dosing intervals on the activity of meropenem. The mean times above the MIC for a bacteriostatic effect were 28.3% for E.coli, 19.7% for K.pneumoniae in the thigh model, 18.2% for K.pneumoniae in the lung model and 21.5% for P.aeruginosa. T>MIC was similar to imipenem and biapenem for E.coli and P.aeruginosa but was lower for meropenem against K.pneumoniae. The authors suggested that, as meropenem tended to have lower MICs than imipenem and biapenem against Enterobacteriacea (e.g. E.coli, Enterobacter cloacae, and K.pneumoniae), it may be more effective in treating infections caused by these organisms.

Table 4.3 summarises the pharmacodynamic studies of meropenem up until the start of the thesis in 2002.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
<th>Antibiotic(s)</th>
<th>Organism(s)</th>
<th>Conclusion of marker of efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vogelman et al (1988)</td>
<td>Neutropenic mouse thigh</td>
<td>Cefazolin, penicillin, ticarcillin G, T &gt; MIC. % of time varies according to drug-organism combination and dosing interval should be no greater than T&gt;MIC plus duration of any post-antibiotic effect.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluckiger, Segessenmann and Gerber (1991)</td>
<td>Neutropenic mouse thigh</td>
<td>Imipenem</td>
<td>E.coli, P.aeruginosa</td>
<td>T&gt;MIC for 70 to 80%</td>
</tr>
<tr>
<td>Craig, Ebert and Watanabe (1993)</td>
<td>Neutropenic mouse thigh and lung</td>
<td>Penicillins, cephalosporins and carbapenems (imipenem biapenem)</td>
<td>Different bacteria with MICs ranging from 0.005 to 256mg/L &amp; 1. lowest with carbapenems (imipenem &amp; biapenem) &amp; highest with cephalosporins. 2. lower against staphylococci than streptococci and Gram negative bacilli 3. lower with the carbapenems, imipenem and biapenem, against P. aeruginosa than with other Gram negative bacilli (27±5). 4. Similar in the lung and thigh models for the strain of K. pneumoniae studied.</td>
<td></td>
</tr>
<tr>
<td>Mouton and den Hollander (1994)</td>
<td>In vitro model</td>
<td>Ceftazidime</td>
<td>P.aeruginosa</td>
<td>T &gt; 4 to 5 x MIC (as continuous infusion) was likely to be more effective than 1 x MIC.</td>
</tr>
<tr>
<td>Walker et al (1994)</td>
<td>Mouse thigh and lung models</td>
<td>Meropenem</td>
<td>E.coli, P.aeruginosa, K.pneumoniae</td>
<td>Maximum bacteriostatic effect varied according to organism (T&gt;MIC 18.2 – 28.3 % of dose interval)</td>
</tr>
</tbody>
</table>

**Table 4.3 Summary of studies to determine the marker of efficacy relating to the use of meropenem (up to 2002)**
<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
<th>Antibiotic(s)</th>
<th>Organism(s)</th>
<th>Conclusion of marker of efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fuentes et al (1995)</td>
<td>Neutropenic mouth thigh</td>
<td>Meropenem</td>
<td><em>E.coli</em>, <em>S.aureus</em>, <em>P.aeruginosa,</em></td>
<td>More than one pharmacokinetic parameter may be related to some strains, which may include T&gt;MIC.</td>
</tr>
<tr>
<td>Bowker et al (1996)</td>
<td><em>In vitro model</em></td>
<td>Meropenem</td>
<td><em>E.coli</em>, <em>S.aureus</em>, <em>P.aeruginosa,</em> <em>Enterobacter</em> spp, <em>Klebsiella</em> spp</td>
<td>Concentration-dependent killing up to 50mg/L Post-antibiotic effect and modified controlled effective regrowth time increased up to 75mg/L</td>
</tr>
<tr>
<td>Andes and Craig (1998)</td>
<td>Neutropenic mouse thigh</td>
<td>Amoxicillin and amoxicillin-clavulanate</td>
<td><em>S.pneumoniae</em></td>
<td>T &gt; MIC = 40% of dosing interval</td>
</tr>
<tr>
<td>Bowker et al (1998)</td>
<td><em>In vitro model</em></td>
<td>Meropenem</td>
<td><em>E.coli</em>, <em>S.aureus</em>, <em>P.aeruginosa</em></td>
<td>T&gt; MIC. % not stated</td>
</tr>
<tr>
<td>Craig (1998)</td>
<td>Neutropenic mouse lung</td>
<td>Cefotaxime</td>
<td><em>K.pneumoniae</em></td>
<td>Bacteriostatic when T&gt;MIC for 30 – 40%. Maximal killing when T &gt; MIC for 60 – 70% of dosage interval</td>
</tr>
<tr>
<td>Tam et al (2002)</td>
<td>20 patients with infection</td>
<td>Cefepime</td>
<td>Gram negative bacteria</td>
<td>Microbiological success 89% when T &gt; MIC was 100%, versus 0% when T&gt; MIC was &lt; 100%, but strongest relationship was T &gt; 4.3 x MIC.</td>
</tr>
</tbody>
</table>

*Table 4.3 continued. Summary of studies to determine the marker of efficacy relating to the use of meropenem (up to 2002)*
4.1.7. Measures of efficacy in pharmacokinetic / pharmacodynamic studies of meropenem in non-burn patient populations

From section 4.1.6, it can be seen that although the percentage of time above the MIC (T>MIC) is likely to be the best marker of efficacy for meropenem, there is no strong evidence of exactly what percentage of the dose interval should be above the MIC. Because of this, pharmacokinetic-pharmacodynamic studies have used different markers. A search of Embase and Medline up until 2002 (the year of commencement of this burns pharmacokinetic study) revealed the following studies where meropenem pharmacokinetics were applied in clinical studies to determine the dosing schedules in different patient populations.

4.1.7.1. Pharmacokinetic / pharmacodynamic studies of meropenem in children, infants and neonates

Blumer et al (1995) measured serum concentrations of meropenem in children to develop a dosing schedule. The dose they suggested was based on the premise that beta-lactam antibiotics needed to be at inhibitory concentrations at the site of infection throughout the dosing interval. No reference is given for this assumption.

Goldstein et al (2001) aimed to determine a suitable dose of meropenem for children and adolescents receiving haemodialysis. Their measure of efficacy was 70% of the dosing interval above the MIC. The MIC they used was 4mg/L - that of P. aeruginosa. The references they used for their measure were review articles (Craig 1997; Craig 1998; Mouton 2000). Goldstein et al (2001) opted for 70% rather than 40 – 50% quoted in some of those reviews because of the relatively immunosuppressed state of the uremic patient.

A study has also been undertaken (Van Enk, Touw and Lafeber 2001) to ascertain an appropriate dosage regimen for meropenem in pre-term neonates. A dose was proposed based on the measure of efficacy being above 4mg/L for half of the dosing interval. The authors stated, without referencing, that this was selected because animal studies showed optimal effect at 30 to 50% of the time above the
MIC and also because standard dosing regimens in adults resulted in a time above the MIC of approximately 50% at an MIC of 4mg/L, the breakpoint for most organisms.

4.1.7.2. Pharmacokinetic / pharmacodynamic studies of meropenem in patients with cystic fibrosis

The first published study of meropenem use in cystic fibrosis patients (Christensson et al. 1998) evaluated a single dose of 15mg/kg (approximately 1g) and concluded that some patients may require doses to be given more frequently than every eight hours, as their serum concentrations dropped below 4mg/L before 3.3 hours. This would mean that concentrations would be below an MIC of 4mg/L for more than 60% of an eight-hourly dose-interval. The rationale for the requirement for the concentration to be above the MIC for at least 40% of the dose interval appears to come from a study of the relationship between pharmacokinetic parameters and efficacy of antibiotics in patients with Gram-negative pneumonia (Schentag 1990).

Bui et al (2001) evaluated meropenem at a dose of 2g 8-hourly in patients with cystic fibrosis. Their pharmacodynamic predictor for a successful outcome was a plasma meropenem concentration above the MIC for at least 40 – 50% of the dosing interval, which was based on three review articles of beta-lactams. The first of these references (Craig 1995) related to cephalosporins only. The second (Drusano and Hutchison 1995) referred to the work discussed in 4.1.5 (Walker et al. 1994), but stated that an organism inhibitory effect was seen with approximately 33 to 40% of the dosing interval covered by drug concentration for carbapenems relative to 50 – 60% of the dosing interval required for penicillins and cephalosporins. The final reference (Craig 1997) also referred to the work by Walker et al (1994) with the only conclusion being that the duration of time that serum levels exceeded the MIC was the important determinant of in vivo efficacy for meropenem. Bui et al (2001) suggested that a dose of 2g every eight hours should be administered to cystic fibrosis patients, especially where the infections were caused by organisms with an MIC close to the breakpoint of 4mg/L.
4.1.7.3. Pharmacokinetic / pharmacodynamic studies of meropenem in critically ill patients

Kitzes-Cohen et al (2002) examined the pharmacokinetics and pharmacodynamics of meropenem in critically ill patients with sepsis. They proposed that a target concentration of four times the MIC during at least 70% of the dosing interval was needed for effective killing, although they then stated that most authors agree that concentration of at least four times the MIC has to be maintained for 40 – 50% of the dosing interval, to achieve clinical effectiveness. They used two references to support their recommendation. Firstly Thalhammer et al (1999) which is discussed below. The second is a review of the pharmacokinetic and pharmacodynamic properties of antimicrobials in respiratory tract infections (Andes 2001). For beta-lactams, the conclusion of that review was that free drug concentrations should exceed the MIC for 40-50% of the dosing interval, but there was no specific mention of any of the carbapenems. The only reference in that review which referred specifically to carbapenems was the conference paper previously discussed (Craig, Ebert and Watanabe 1993) that concluded that that T>MIC (mean % of dose interval ± SD) was lowest with the carbapenems.

Thalhammer et al (1999) compared continuous and intermittent infusion of meropenem in critically ill patients. They stated that most authors agreed that T>MIC needed to be at least 40 – 50% of the dosing interval to achieve clinical effectiveness, but that maximal killing was seen when T>MIC was at least 60 – 70%. Their rationale for this appears to be the work already discussed (Craig 1998) on cefotaxime against K. pneumoniae in the lungs of neutropenic mice, where maximal killing was approached when levels were above the MIC for 60 – 70% of the time.
4.1.7.4. Pharmacokinetic / pharmacodynamic studies of meropenem in patients who require renal support

Thalhammer *et al* (1998) were also one of several groups of investigators who determined the dose of meropenem in critically ill patients requiring renal support. In their study of patients receiving continuous venovenous haemofiltration, they stated that as beta-lactam and carbapenem antibiotics were thought to act only if their concentrations are well above the MIC for the pathogen, these levels should be maintained for the maximum amount of time. They also suggested that other authors had proposed that maximum efficacy occurred when meropenem serum concentrations were four- to eightfold the target MIC<sub>90</sub> of the target pathogen. No references were given to support these recommendations. They recommended their dose of 1g every eight hours based on the fact that it resulted in a serum concentration of 12mg/L after 50% of the dosing interval.

Kruger *et al* (1998) elected to administer meropenem to critically ill patients requiring renal support at a dose of 1g every twelve hours. This was thought to be a suitable dose as mean the plasma concentrations exceeded MICs for pathogens classed as susceptible (less than 4mg/L) or of intermediate susceptibility (up to 8mg/L) for the whole dosing interval. For more susceptible bacteria, the authors suggested that a lower dose may be sufficient.

Another study (*Giles et al*. 2000) adopted 4mg/L as their target concentration as although for meropenem the MIC<sub>90</sub>s is less than 0.5mg/L for most organisms, the MIC<sub>90</sub> for *P.aeruginosa* is 4mg/L. They proposed that the optimum carbapenem regimen would probably be one where concentrations were above the MIC for the whole dosing interval. Their references for this were two review articles. The first (*Mouton and Van den Anker* 1995), proposes that for beta-lactams in general, the time above the MIC should be maximised, but for meropenem, concentrations may not need to be above the MIC for the whole dose interval because of its post-antibiotic effect. The second (*Gould* 1997) discussed the pharmacodynamics of all antibiotics.
Ververs et al (2000) also aimed for the serum concentration to be above the MIC for 100% of the dose interval, but gave no references to support this. They stated that they did not use 33 to 40% as suggested in the conference paper presented by Craig, Ebert and Watanabe (1993) as this was based on laboratory and animal data.

Tedeger et al (1999) also opted to maximise the time above the MIC. They aimed for 12mg/L as this was in excess of the MIC for intermediately resistant bacteria (8mg/L). Because of limited good evidence for maximum efficacy being less than 100% of T>MIC, they chose the maximum time particularly as they were treating critically ill patients.

Meyer at el (1999) measured serum concentrations in a single patient with multiorgan failure undergoing continuous venovenous hemodiafiltration\textsuperscript{14}. Based on the results for that patient they recommended a dose of 1g every twelve hours as this dosing interval was approximately four half-lives and the twelve-hour trough level of 4.5mg/L exceeded the MIC\textsubscript{90}\textsuperscript{15} for most susceptible organisms.

\textit{4.1.7.5. Pharmacokinetic / pharmacodynamic studies of meropenem in patients with neutropenia}

In a study of meropenem administered to febrile neutropenic patients, Nyhlen, Ljungberg and Nilsson-Ehle (1997) based their measure of efficacy on the T>MIC, and used MIC\textsubscript{90}s from the literature of three pathogens; 4.0mg/L for \textit{P.aeruginosa}, 0.25mg/L for \textit{S.aureus} and 0.06mg/L for \textit{E.coli}. Whilst they did not give a specific percentage as their goal, they suggested that more frequent dosing, or even change to continuous infusion, may be better for patients with less susceptible pathogens. This was because they found that the T>MIC was, on average, only half of the dosing interval for the MIC\textsubscript{90} of \textit{P.aeruginosa} (range approximately 30 to 100%).

\textsuperscript{14} Veno-venous filtration is a process similar to haemodialysis where a patient’s blood flows out of a vein through a tube, passing through a filter where waste products and water are removed. Replacement fluid is then added and the blood is returned back to the body.

\textsuperscript{15} The MIC\textsubscript{90} is the MIC required to inhibit the growth of 90% of organisms.
4.1.7.6. Summary and conclusions from review of pharmacokinetic / pharmacodynamic studies of meropenem in patient populations

Table 4.4 summarises the dose finding studies for meropenem in patient populations. It can be seen that most authors agree that it is the percentage of the dose interval where serum concentrations exceed the MIC that is the best measure of clinical effectiveness. This is supported by the data presented in Section 4.1.5. However, there is no consensus as to the proportion of the dose interval that is required to be above the MIC for maximal efficacy, with figures adopted by dose-finding studies ranging from 40 to 100%. None of the dose-finding studies measured patient outcome.
<table>
<thead>
<tr>
<th>Study</th>
<th>Patient group</th>
<th>T &gt; MIC selected</th>
<th>Target concentration</th>
<th>Dose recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blumer et al (1995)</td>
<td>Children</td>
<td>100%</td>
<td>Up to 2mg/L (measured MIC)</td>
<td>20mg/kg every eight hours</td>
</tr>
<tr>
<td>Goldstein et al (2001)</td>
<td>Children &amp; adolescents receiving haemodialysis</td>
<td>70%</td>
<td>4mg/L (MIC)</td>
<td>25mg/kg/day or 40mg/kg on alternate days</td>
</tr>
<tr>
<td>Van Enk, Touw and Lafeber (2001)</td>
<td>Pre-term neonates</td>
<td>50%</td>
<td>4mg/L (breakpoint)</td>
<td>15mg/kg every twelve hours</td>
</tr>
<tr>
<td>Bui et al (2001)</td>
<td>Cystic fibrosis</td>
<td>40 – 50%</td>
<td>Up to 4mg/L (MIC)</td>
<td>2g every eight hours</td>
</tr>
<tr>
<td>Christensson et al (1998)</td>
<td>Cystic fibrosis</td>
<td></td>
<td></td>
<td>Shorter dose intervals may be required</td>
</tr>
<tr>
<td>Kitzes-Cohen et al (2002)</td>
<td>Critically ill</td>
<td>40 – 50%</td>
<td>Four times the MIC. MICs were up to 3mg/L.</td>
<td>None</td>
</tr>
<tr>
<td>Thalhammer et al (1999)</td>
<td>Critically ill</td>
<td></td>
<td>Doses used thought to be sufficient as T&gt;MIC was 100%</td>
<td>Up to 8mg/L</td>
</tr>
<tr>
<td>Thalhammer et al (1998)</td>
<td>Critically ill receiving continuous venovenous hemofiltration</td>
<td>50%</td>
<td>12mg/L</td>
<td>1g every eight hours</td>
</tr>
<tr>
<td>Krueger et al (1998)</td>
<td>Critically ill patients receiving continuous hemodiafiltration</td>
<td></td>
<td>Doses used thought to be sufficient as T&gt;MIC was 100%</td>
<td>Up to 8mg/L</td>
</tr>
<tr>
<td>Giles et al (2000)</td>
<td>Critically ill receiving continuous venovenous hemofiltration or hemodiafiltration</td>
<td>100%</td>
<td>4mg/L</td>
<td>1g every twelve hours</td>
</tr>
<tr>
<td>Meyer et al (1999)</td>
<td>One patient undergoing continuous venovenous hemodiafiltration</td>
<td>100%</td>
<td>Trough level (4.5mg/L) above MIC₉₀ for most susceptible organisms</td>
<td>1g every twelve hours</td>
</tr>
</tbody>
</table>

Table 4.4 Summary of markers of efficacy selected in dose-finding studies of meropenem
<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient group</th>
<th>T &gt; MIC selected</th>
<th>MIC selected</th>
<th>Dose recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tegeder et al (1999)</td>
<td>Critically ill undergoing continuous venovenous hemofiltration</td>
<td>100%</td>
<td>12mg/L</td>
<td>Double the dose required for anuric patients</td>
</tr>
<tr>
<td>Ververs et al (2000)</td>
<td>Critically ill receiving continuous venovenous hemofiltration</td>
<td>100%</td>
<td>2mg/L</td>
<td>500mg every twelve hours</td>
</tr>
<tr>
<td>Nyhlen, Ljungberg and Nilsson-Ehle (1997)</td>
<td>Febrile neutropenia</td>
<td>T &gt; MIC – percentage not stated</td>
<td>According to published MIC₉₀s for common pathogens.</td>
<td>Six or eight hourly dosing</td>
</tr>
</tbody>
</table>

Table 4.4 continued. Summary of markers of efficacy selected in dose-finding studies of meropenem

### 4.2. Aims and objectives

As outlined in Chapter 1, Section 1.11 the aim of this study was to investigate the pharmacokinetic parameters of antibiotics when administered to patients with major burns and to produce dosing guidelines for the use of these antibiotics.

Objectives were:

- To measure the serum concentrations of meropenem in adults with major burns (>15% total body surface area) receiving this antibiotic for treatment of severe infections.
- To compare the serum concentrations with those required to treat likely infections.
- To calculate pharmacokinetic parameters such as volume of distribution, clearance and elimination half-life.
- To compare pharmacokinetic parameters calculated in this study of severely burned patients with other populations.
• To investigate the influence of patient factors on the serum concentrations and pharmacokinetic parameters.
• To produce dosage guidelines for the use of meropenem in adults with major burns.

4.3. Materials and Methods

The methodology for the pharmacokinetic study of meropenem is outlined in Chapter 3. Meropenem was administered over 5 minutes in line with guidelines developed by the Researcher in the role of clinical pharmacist.

For this clinical study the measure of efficacy selected was for serum concentrations to be above 4mg/L for at least 40% of the dose interval at steady-state. This was for several reasons:

1. Studies of the pharmacokinetics of meropenem in healthy volunteers (Drusano and Hutchison 1995) show the concentration dropping below 4mg/L between 40 – 50% of the dose-interval following a dose of 1g. Drusano and Hutchison (1995) concluded that based on concentrations 4 hours after a 1g dose, all pathogens with an MIC of less than 4mg/L would be effectively treated, and that even for seriously ill infected patients, 1g of meropenem every eight hours would provide adequate empiric cover for the vast majority of pathogens seen in hospital patients. This recommendation was based on the assumption that meropenem pharmacokinetics are the same in patient populations as healthy volunteers. This is known not to be the case in some clinical conditions such as cystic fibrosis (Christensson et al. 1998) and may also be the case for patients with severe burns. However it would seem logical to uses doses that would achieve a similar serum concentration profile when treating patients with burns.

2. Animal studies (Drusano 2003) suggest that, for carbapenems, maximal killing is reached when T>MIC of 40%.
3. Ideally the target serum concentration would be adjusted according to the MIC of the infecting organism. However, treatment is often empiric, and even when the infecting organism is known, it is unlikely that its MIC will be measured. For meropenem, published MICs of likely pathogens are usually well below 4mg/L, but *P. aeruginosa* may be 4mg/L (Pfaller and Jones 1997). Therefore in the absence of a known MIC, a serum concentration of 4mg/L would seem to be a rational target.

4. The susceptibility breakpoint\(^\text{16}\) for meropenem was 4mg/L at the time of commencement of the study (BSAC 2002). Susceptibility breakpoints for various antimicrobial / organism combinations are based upon the highest MIC for which serum concentrations would still remain above the MIC for 40% of the time of a standard dosing regimen (Andes 2001). This assumes the pharmacokinetic profile of the antibiotic is the same as for healthy subjects.

5. Animal studies have indicated that the concentration in burn fluid exudate is similar to the serum concentrations attained (Yoshida et al. 1993b), and hence a target of at least 4mg/L is likely to result in therapeutic concentrations in the burn wound, the most likely source of infection.

It is acknowledged that this may be a conservative target, and some other pharmacokinetic studies have selected both a T>MIC of more than 40% and a target concentration of greater than 4mg/ml (Table 4.4). However, as outlined in Section 4.1.5 and the points above, based on the evidence available in 2002 the measure would seem to be appropriate. In the Discussion section of this chapter (Section 4.5.3), data published since 2002 will be reviewed, to determine whether this marker of efficacy represents current practice.

---

\(^{16}\) A discriminating concentration used in the interpretation of results of susceptibility testing to define isolates as susceptible, intermediate or resistant. In practice this means that if an organism is classed as susceptible to an antimicrobial agent, the MIC is no greater than the breakpoint, but may be considerably lower.
4.4. Results

4.4.1. Demographics

Twelve patients were successfully recruited to the meropenem arm of the study, resulting in 20 meropenem data sets (Table 4.5). The mean age of the study group was 46 years, the youngest being 27 years and the oldest 73 years. Mean percentage total body surface area (TBSA) burn was 43%, with the range from 20% up to 80%. Seven patients were male, and seven also had an inhalational injury. Causes of burns were varied and included accidental explosion, hot water and assault, although all but two were flame burns. All patients were mechanically ventilated, spending a mean of 53 days in intensive care, but the range was broad (19 to 126 days). None received renal replacement therapy.

From Table 4.5, it can be seen that the mean age plus % TBSA burn was 90 (range 65 to 115). None of the seven patients who survived their injury had a combined age plus % TBSA of over 100 (mean 80.7). All three patients with a combined sum of over 100 died, together with two patients whose scores were between 90 and 100 (mean of those who died was 103.2). The combined sums of the patients who survived were significantly lower than those who died (p<0.01).

The mean ABSI score was 9.3 (range 5-12). The mean score of the patients who survived was lower than those who died (8.9 vs 10.0), but the difference was not significant (p = 0.24).
<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Sex</th>
<th>Age</th>
<th>Cause of burn</th>
<th>Type of burn</th>
<th>% TBSA burn</th>
<th>Inhalation injury</th>
<th>ABSI Score*</th>
<th>Outcome</th>
<th>Length of stay in ITU (days)</th>
<th>Serum Cr (μmol/L)</th>
<th>CrCl (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>27</td>
<td>Gas fire explosion on house boat</td>
<td>Flame</td>
<td>50</td>
<td>N</td>
<td>9</td>
<td>Survived</td>
<td>60</td>
<td>26</td>
<td>307</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>38</td>
<td>Unconfirmed</td>
<td>Chemical</td>
<td>70</td>
<td>N</td>
<td>10</td>
<td>Died</td>
<td>119</td>
<td>28</td>
<td>201</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>62</td>
<td>Explosion in shed</td>
<td>Flame</td>
<td>32</td>
<td>Y</td>
<td>10</td>
<td>Survived</td>
<td>38</td>
<td>50</td>
<td>219</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>73</td>
<td>House fire</td>
<td>Flame</td>
<td>34</td>
<td>Y</td>
<td>10</td>
<td>Died</td>
<td>43</td>
<td>112</td>
<td>64</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>45</td>
<td>Hot bath</td>
<td>Scald</td>
<td>20</td>
<td>N</td>
<td>7</td>
<td>Survived</td>
<td>41</td>
<td>42</td>
<td>259</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>35</td>
<td>Inflammable liquid</td>
<td>Flame</td>
<td>80</td>
<td>Y</td>
<td>12</td>
<td>Died</td>
<td>73</td>
<td>35</td>
<td>332</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>37</td>
<td>Assault – clothes set alight</td>
<td>Flame</td>
<td>35</td>
<td>N</td>
<td>5</td>
<td>Survived</td>
<td>31</td>
<td>42</td>
<td>196</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>27</td>
<td>Caravan explosion</td>
<td>Flame</td>
<td>52</td>
<td>Y</td>
<td>10</td>
<td>Survived</td>
<td>20</td>
<td>54</td>
<td>190</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>40</td>
<td>Assault - petrol</td>
<td>Flame</td>
<td>53</td>
<td>Y</td>
<td>11</td>
<td>Survived</td>
<td>40</td>
<td>42</td>
<td>161</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>59</td>
<td>Candle ignited clothes</td>
<td>Flame</td>
<td>32</td>
<td>N</td>
<td>9</td>
<td>Died</td>
<td>126</td>
<td>51</td>
<td>164</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>70</td>
<td>House fire</td>
<td>Flame</td>
<td>25</td>
<td>Y</td>
<td>9</td>
<td>Died</td>
<td>29</td>
<td>59</td>
<td>106</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>39</td>
<td>House fire</td>
<td>Flame</td>
<td>46</td>
<td>Y</td>
<td>10</td>
<td>Survived</td>
<td>19</td>
<td>76</td>
<td>168</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>43</td>
<td></td>
<td>9.3</td>
<td></td>
<td>53</td>
<td>51</td>
<td>197</td>
</tr>
<tr>
<td>Range</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20–80</td>
<td></td>
<td>5 – 12</td>
<td></td>
<td>19–126</td>
<td>26–112</td>
<td>64–332</td>
</tr>
</tbody>
</table>

Table 4.5. Patient demographics of meropenem study
<table>
<thead>
<tr>
<th>* ABSI Score</th>
<th>Threat to life</th>
<th>Probability of Survival</th>
<th>Score</th>
<th>Threat to life</th>
<th>Probability of Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 – 3</td>
<td>Very Low</td>
<td>0.99</td>
<td>8 - 9</td>
<td>Serious</td>
<td>0.5 – 0.7</td>
</tr>
<tr>
<td>4 – 5</td>
<td>Moderate</td>
<td>0.98</td>
<td>10 – 11</td>
<td>Severe</td>
<td>0.2 – 0.4</td>
</tr>
<tr>
<td>6 – 7</td>
<td>Moderately severe</td>
<td>0.8 – 0.9</td>
<td>12 - 13</td>
<td>Maximum</td>
<td>≤ 0.1</td>
</tr>
</tbody>
</table>

Table 4.5 continued. Patient demographics of meropenem study

Table 4.5 illustrates the demographics of the patients recruited to the meropenem arm of the study. Cr = measured creatinine when the first sample was taken, and CrCl is the estimated creatinine clearance calculated by the Cockcroft and Gault Equation\(^\text{17}\) (Cockcroft and Gault 1976).

---

\(^{17}\) The Cockcroft and Gault Equation is \((140 – \text{age in years}) \times \text{bodyweight (kg)} / \text{serum creatinine (mmol/L)}\). This figure is multiplied by 1.23 for males and 1.04 for females.
There was a positive correlation between patient age and serum creatinine \((r^2 = 0.312, p = 0.011)\) and negative correlations between age and creatinine clearance as estimated by the Cockcroft and Gault equation \((Cockcroft and Gault 1976) (r^2 = 0.971, p = < 0.001)\) and between age and the total percentage burn surface area \((r^2 = 0.439, p = 0.002)\). Whilst these were all significant, only the correlation between age and estimated creatinine clearance was strong. No other significant correlations were noted.

### 4.4.2. Infecting organisms

Many pathogens were identified from several sites including skin / wounds, blood, sputum, and central venous pressure (CVP) tips\(^ {18} \) around the time of infection. Pathogens identified included *Staphylococcus aureus*, *Pseudomonas aeruginosa*, coagulase-negative staphylococci, *Enterococcus* sp., *Enterobacter cloacae*, *Klebsiella* spp, *Acinetobacter* spp., *Bacillus cereus*, and *Stenotrophomonas maltophilia* (Table 4.6). There were no reports of intermediate sensitivity or resistance to meropenem, although there was one report of resistance of *P.aeruginosa* to imipenem from a wound swab in a later infection in one patient. It is therefore likely that this strain would have also been resistant to meropenem.

---

\(^{18}\) A CVP tip is the tip of a catheter placed into a large vein. The catheter is used for measuring the central venous pressure, and also for the administration medicines and the taking of blood.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Site</th>
<th>Microbes identified</th>
<th>Sensitive to</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Blood</td>
<td><em>Acinetobacter baumannii</em></td>
<td>IMI, COL, AMI, MER</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Pseudomonas spp</em></td>
<td>CIP, GEN, TAZ, MER, CEFTAZ</td>
</tr>
<tr>
<td></td>
<td>CVP</td>
<td><em>A. baumannii</em></td>
<td>GEN, IMI, COL, AMI, MER</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Pseudomonas aeruginosa</em></td>
<td>CIP, GEN, CEFTAZ</td>
</tr>
<tr>
<td></td>
<td>CNS</td>
<td></td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Wound</td>
<td><em>Enterococcus spp</em></td>
<td>AMOX</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>P. aeruginosa</em></td>
<td>CIP, GEN, CEFTAZ</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>A. baumannii</em></td>
<td>IMI, COL, AMI, MER, TRIM, GEN, CEFUR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Coliforms</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Candida spp</em> (not albicans)*</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Sputum</td>
<td><em>S. maltophilia</em></td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Pseudomonas spp</em></td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Sputum</td>
<td><em>Acinetobacter spp</em></td>
<td>IMI, AMI, MER</td>
</tr>
<tr>
<td></td>
<td>Wound</td>
<td>Coliforms</td>
<td>MER</td>
</tr>
<tr>
<td>3</td>
<td>Blood</td>
<td><em>CNS</em></td>
<td>FUS.</td>
</tr>
<tr>
<td></td>
<td>Sputum</td>
<td><em>CNS</em></td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Skin, blood, sputum</td>
<td>Diphteroids</td>
<td>TET, AMOX, VANC</td>
</tr>
<tr>
<td>4</td>
<td>Sputum</td>
<td><em>Enterobacter spp</em></td>
<td>Carbapenems</td>
</tr>
<tr>
<td></td>
<td>BAL</td>
<td><em>S. aureus</em></td>
<td>TET, FLUC, ERY</td>
</tr>
<tr>
<td></td>
<td>Blood</td>
<td>Group D strep (enterococcus)</td>
<td>AMOX, VANC</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Klebsiella oxytoca</em></td>
<td>TRIM, GEN, TAZ, CEFUR, MER</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>E. coli</em></td>
<td>TRIM, GEN, TAZ, CEFUR, MER</td>
</tr>
<tr>
<td></td>
<td>BAL</td>
<td><em>Candida albicans</em></td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>BAL</td>
<td><em>H. influenzae</em></td>
<td>TRIM, COAMOX, CEFUR</td>
</tr>
<tr>
<td></td>
<td>Skin</td>
<td><em>CNS</em></td>
<td>GEN, TET</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Enterococcus spp</em></td>
<td>AMOX</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Coliforms</td>
<td>GEN, CEFUR, TRIM</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Candida spp</em></td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Catheter tip</td>
<td><em>CNS</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Catheter tip</td>
<td>Coliforms</td>
<td>TRIM, COAMOX, TAZ, MER</td>
</tr>
</tbody>
</table>

*Table 4.6 Microbiology of the organisms identified*
<table>
<thead>
<tr>
<th>Patient</th>
<th>Site</th>
<th>Microbes identified</th>
<th>Sensitive to</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Blood</td>
<td>CNS</td>
<td>VANC</td>
</tr>
<tr>
<td></td>
<td>Sputum</td>
<td>P. aeruginosa</td>
<td>GEN, IMI, TAZ</td>
</tr>
<tr>
<td></td>
<td>Wound</td>
<td>E. coli</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CVP Tip</td>
<td><em>Candida albicans</em></td>
<td>GEN, CIP, TAZ</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>S. aureus</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>A. baumannii</em></td>
<td>COAMOX, GEN, IMI, TAZ</td>
</tr>
<tr>
<td>6</td>
<td>Blood</td>
<td><em>P. aeruginosa</em></td>
<td>GEN, CIP, IMI, TAZ</td>
</tr>
<tr>
<td></td>
<td>Sputum</td>
<td><em>Candida albicans</em></td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>CVP tip</td>
<td><em>P. aeruginosa</em></td>
<td>GEN, TAZ</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Klebsiella sp</em></td>
<td>IMI</td>
</tr>
<tr>
<td></td>
<td>Skin</td>
<td><em>CNS</em></td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Candida albicans</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Skin</td>
<td><em>Klebsiella pneumoniae</em></td>
<td>COAMOX, IMI, TAZ</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>P. aeruginosa</em></td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Candida spp.</em></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Sputum</td>
<td><em>Enterobacter cloacae</em></td>
<td>GEN, IMI</td>
</tr>
<tr>
<td></td>
<td>Blood</td>
<td>CNS</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Blood</td>
<td><em>Bacillus cereus</em></td>
<td>ERY, CIP</td>
</tr>
<tr>
<td>8</td>
<td>Sputum</td>
<td><em>S. maltophilia</em></td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Skin</td>
<td><em>Candida albicans</em></td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>CNS</em></td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Stenotrophomonas maltophilia</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Enterobacter cloacae</em></td>
<td>NR</td>
</tr>
<tr>
<td>9</td>
<td>Sputum</td>
<td><em>S. maltophilia</em></td>
<td>MER, TAZ, CIP</td>
</tr>
<tr>
<td></td>
<td>Blood</td>
<td><em>Enterococcus faecalis</em></td>
<td>AMP, AMOX, VANC, LIN</td>
</tr>
<tr>
<td></td>
<td>Blood</td>
<td><em>Enterobacter cloacae</em></td>
<td>GEN, CIP</td>
</tr>
<tr>
<td></td>
<td>Blood</td>
<td><em>B. cereus</em></td>
<td>CIP</td>
</tr>
<tr>
<td></td>
<td>CVP Tip</td>
<td><em>C. albicans</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Skin</td>
<td><em>Enterococcus spp</em></td>
<td>AMP, AMOX</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Bacillus cereus</em></td>
<td>CIP</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>MRSA</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>C. albicans</em></td>
<td></td>
</tr>
</tbody>
</table>

*Table 4.6 continued. Microbiology of the organisms identified*
<table>
<thead>
<tr>
<th>Patient</th>
<th>Site</th>
<th>Microbes identified</th>
<th>Sensitive to</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Sputum</td>
<td><em>H. influenzae</em></td>
<td>AMP, AMOX, CIP</td>
</tr>
<tr>
<td></td>
<td>Blood</td>
<td>CNS</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Sputum</td>
<td><em>P. aeruginosa</em></td>
<td>GEN, CIP</td>
</tr>
<tr>
<td></td>
<td>Skin</td>
<td><em>S. aureus, MRSA</em></td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Proteus mirabilis</em></td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Enterococcus spp</em></td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>E. coli</em></td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>C. albicans</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CVP tip</td>
<td>MRSA</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Blood</td>
<td><em>Enterococcus faecium</em></td>
<td>GEN, VANC</td>
</tr>
<tr>
<td></td>
<td>Blood</td>
<td>CNS</td>
<td>VANC</td>
</tr>
<tr>
<td>12</td>
<td>Sputum</td>
<td><em>S. aureus</em></td>
<td>ERY, FLUCI</td>
</tr>
</tbody>
</table>

*Table 4.6 continued. Microbiology of the organisms identified*

NR = not reported on results to clinicians, BAL – broncho-alveolar lavage CNS = coagulase negative staphylococci, AMOX = amoxicillin, AMP = ampicillin, CEFTAZ = ceftazidime, CEFUROX = cefuroxime, CIPRO = ciprofloxacin, COL = colistin, COAMOX = co-amoxiclav, ERY = erythromycin, GENT = gentamicin, IMI = imipenem, LIN = linezolid, MER = meropenem, VANC = vancomycin

The data in Table 4.6 was obtained from the microbiology reports for each patient. It is likely that some antibiotics (e.g. ones generally reserved for the treatment of multidrug resistant infections) that organisms were susceptible to were not reported on the standard forms. Instead the information would have been retained by the microbiologist so would be commenced only on specialist advice.

### 4.4.3. Relationship between dose and effect

All patients were commenced on a dose of 1g every eight hours. Figure 4.4 shows a wide inter-patient variation between the serum concentrations at this dose.
Figure 4.4. Concentrations of meropenem in serum at steady state for patients receiving a starting dose of 1g every eight hours.

Figure 4.4 shows the first set of serum concentrations measured for each patient when commencing on a dose of 1g every eight hours. The dose was judged to be efficacious if the serum concentration was above 4mg/L for at least 40% of the dose interval (i.e. for at least 3.2 hours).

Five of the twelve patients were estimated to have serum concentrations at or above 4mg/L at 3.2 hours i.e. for 40% of the dose interval when receiving the standard dose of 1g every eight hours. In accordance with the measure of efficacy selected, these five patients did not require a dose increase. The other seven had a dose increased to 1g every six hours; and two of these required a further increase to 1g every four hours (Table 4.7).
<table>
<thead>
<tr>
<th>Patient number (course number)</th>
<th>Total length of course</th>
<th>Starting dose</th>
<th>% of dose interval above 4mg/L</th>
<th>Dose changed to</th>
<th>% of dose interval above 4mg/L</th>
<th>Dose changed to</th>
<th>% of dose interval above 4mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (1)</td>
<td>10 days</td>
<td>1g eight-hourly</td>
<td>35</td>
<td>1g six-hourly</td>
<td>N.M.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 (1)</td>
<td>See note 1</td>
<td>1g eight-hourly</td>
<td>38</td>
<td>1g six-hourly</td>
<td>N.M.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 (2)</td>
<td>9 days</td>
<td>2g eight-hourly</td>
<td>90</td>
<td>1g six-hourly</td>
<td>N.M.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 (3)</td>
<td>5 days*</td>
<td>1g six-hourly</td>
<td>55</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 (1)</td>
<td>6 days</td>
<td>1g eight-hourly</td>
<td>75</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 (1)</td>
<td>10 days</td>
<td>1g eight-hourly</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 (1)</td>
<td>7 days</td>
<td>1g eight-hourly</td>
<td>27</td>
<td>1g six-hourly</td>
<td>N.M.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 (1)</td>
<td>11 days</td>
<td>1g eight-hourly</td>
<td>15</td>
<td>1g six-hourly</td>
<td>25</td>
<td>1g four-hourly</td>
<td>100</td>
</tr>
<tr>
<td>6 (2)</td>
<td>5 days</td>
<td>1g six-hourly</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 (1)</td>
<td>6 days</td>
<td>1g eight-hourly</td>
<td>33</td>
<td>See note 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 (1)</td>
<td>12 days</td>
<td>1g eight-hourly</td>
<td>27</td>
<td>1g six-hourly</td>
<td>See note 3</td>
<td>1g four-hourly</td>
<td>40</td>
</tr>
<tr>
<td>9 (1)</td>
<td>8 days</td>
<td>1g eight-hourly</td>
<td>38</td>
<td>1g six-hourly</td>
<td>N.M.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 (2)</td>
<td>6 days</td>
<td>1g eight-hourly</td>
<td>See note 4</td>
<td>1g six-hourly</td>
<td>60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 (1)</td>
<td>10 days</td>
<td>1g eight-hourly</td>
<td>60</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 (2)</td>
<td>8 days</td>
<td>1g eight-hourly</td>
<td>50</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11 (1)</td>
<td>7 days</td>
<td>1g eight-hourly</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 (1)</td>
<td>7 days</td>
<td>1g eight-hourly</td>
<td>40%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4.7. Doses received and estimated percentage of the dose interval above 4mg/L

N.M. Not measured. Note 1. Patient notes not available to obtain / confirm this information.
Note 2. Dose not increased as course stopped on day of sampling. Note 3. Dose increased to six hourly for 1 day, then on further consideration was increased to four-hourly before any sampling took place.

Note 4. Dose increased before sampling took place on the advice of the pharmacist

The percentage of the dose interval was visually estimated by plotting a logarithmic graph of concentration vs time.

### 4.4.4. Meropenem pharmacokinetics

There was large variation in the pharmacokinetic parameters calculated for the patients included in this study (Table 4.8).

The pharmacokinetics of meropenem in this study visually appeared to best fit a two-compartment model (i.e. a distribution phase followed by an elimination phase), with a distribution phase of up to 2 hours. As stated in Chapter 3, Section 3.12.1 the non-compartmental model was applied as there were too few samples taken during the distribution phase (so minimising the amount of blood that needed to be taken from each patient) for a two-compartment model to be used.
<table>
<thead>
<tr>
<th>Pt no (course no)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (mg/L)</th>
<th>AUC&lt;sub&gt;0-∞&lt;/sub&gt; (mg/L.h)</th>
<th>Elimination t&lt;sub&gt;1/2&lt;/sub&gt; (h)</th>
<th>V (L)</th>
<th>V (L/kg)</th>
<th>CL (L/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1g 8-hourly</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (1)</td>
<td>14.30</td>
<td>36.47</td>
<td>2.21</td>
<td>87.57</td>
<td>1.29</td>
<td>27.42</td>
</tr>
<tr>
<td>2 (1)</td>
<td>21.00</td>
<td>39.37</td>
<td>1.80</td>
<td>65.95</td>
<td>1.24</td>
<td>25.40</td>
</tr>
<tr>
<td>3 (1)</td>
<td>22.80</td>
<td>77.92</td>
<td>2.66</td>
<td>49.28</td>
<td>0.43</td>
<td>12.83</td>
</tr>
<tr>
<td>4 (1)</td>
<td>27.80</td>
<td>129.72</td>
<td>4.04</td>
<td>44.92</td>
<td>0.52</td>
<td>7.71</td>
</tr>
<tr>
<td>5 (1)</td>
<td>11.20</td>
<td>28.00</td>
<td>2.06</td>
<td>105.99</td>
<td>1.14</td>
<td>35.72</td>
</tr>
<tr>
<td>6 (1)</td>
<td>9.20</td>
<td>20.77</td>
<td>1.41</td>
<td>97.64</td>
<td>1.08</td>
<td>48.14</td>
</tr>
<tr>
<td>7 (1)</td>
<td>44.40</td>
<td>74.49</td>
<td>0.74</td>
<td>14.39</td>
<td>0.22</td>
<td>13.42</td>
</tr>
<tr>
<td>8 (1)</td>
<td>19.90</td>
<td>29.94</td>
<td>1.09</td>
<td>52.68</td>
<td>0.71</td>
<td>33.40</td>
</tr>
<tr>
<td>9 (1)</td>
<td>28.10</td>
<td>50.78</td>
<td>1.51</td>
<td>42.92</td>
<td>0.66</td>
<td>19.69</td>
</tr>
<tr>
<td>10 (1)</td>
<td>41.50</td>
<td>98.26</td>
<td>4.10</td>
<td>60.20</td>
<td>0.61</td>
<td>10.18</td>
</tr>
<tr>
<td>10 (2)</td>
<td>22.50</td>
<td>59.35</td>
<td>2.35</td>
<td>57.07</td>
<td>0.82</td>
<td>16.85</td>
</tr>
<tr>
<td>11 (1)</td>
<td>40.20</td>
<td>219.93</td>
<td>4.07</td>
<td>26.73</td>
<td>0.31</td>
<td>4.55</td>
</tr>
<tr>
<td>12 (1)</td>
<td>22.30</td>
<td>44.60</td>
<td>1.83</td>
<td>59.15</td>
<td>0.57</td>
<td>22.42</td>
</tr>
<tr>
<td>Mean</td>
<td>25.02</td>
<td>69.97</td>
<td>2.30</td>
<td>58.81</td>
<td>0.74</td>
<td>21.36</td>
</tr>
<tr>
<td>S.D.</td>
<td>11.23</td>
<td>54.70</td>
<td>1.13</td>
<td>26.13</td>
<td>0.35</td>
<td>12.50</td>
</tr>
</tbody>
</table>

| 1g 6-hourly      |                      |                          |                           |      |         |        |
| 2 (3)            | 26.60                | 53.41                    | 1.33                      | 35.91| 0.67    | 18.72  |
| 6 (1)            | 12.40                | 24.45                    | 1.60                      | 94.54| 0.95    | 40.91  |
| 6 (2)            | 26.60                | 91.96                    | 2.82                      | 44.23| 0.52    | 10.87  |
| 9 (2)            | 42.00                | 81.28                    | 1.53                      | 27.10| 0.36    | 12.30  |
| Mean             | 26.90                | 62.78                    | 1.82                      | 50.45| 0.63    | 20.70  |
| S.D.             | 12.09                | 30.28                    | 0.68                      | 30.22| 0.25    | 13.90  |

| 1g 4-hourly      |                      |                          |                           |      |         |        |
| 6 (1)            | 17.40                | 55.79                    | 3.48                      | 90.07| 0.9     | 17.93  |
| 8 (1)            | 39.10                | 60.43                    | 0.66                      | 15.71| 0.21    | 16.55  |

| 2g-8-hourly      |                      |                          |                           |      |         |        |
| 2 (2)            | 79.20                | 161.65                   | 2.29                      | 40.95| 0.63    | 12.37  |

**All results**

| Mean | -     | -     | 2.18  | 55.65 | 0.69   | 20.37  |
| S.D. | -     | -     | 1.06  | 27.31 | 0.32   | 11.59  |

*Table 4.8. Pharmacokinetic parameters calculated for meropenem*

The mean half-life, volume of distribution and clearance values calculated in this study were compared with those published for other populations (Table 4.9). All data is from subjects without renal impairment.
<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Elimination half-life (h)</th>
<th>Clearance (L/hr)</th>
<th>Volume of distribution (L)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burns patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>2.18 ± 1.06</td>
<td>20.37 ± 11.59</td>
<td>55.65 ± 27.31</td>
<td>This study</td>
</tr>
<tr>
<td>28</td>
<td>2.1 ± 0.71</td>
<td>12.00 ± 3.04</td>
<td>20.75 ± 5.35**</td>
<td>Lin et al (2004a)</td>
</tr>
<tr>
<td>P¹</td>
<td>0.814</td>
<td>0.031*</td>
<td>&lt; 0.001*</td>
<td></td>
</tr>
<tr>
<td>Healthy young men</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0.96 ± 0.05</td>
<td>15.24 ± 0.96</td>
<td>17.8 ± 0.7</td>
<td>Bax et al (1999)</td>
</tr>
<tr>
<td>6</td>
<td>1.02 ± 0.13</td>
<td>12.6 ± 1.7</td>
<td>15.7 ± 1.4</td>
<td>Kelly et al (1995)</td>
</tr>
<tr>
<td>9</td>
<td>0.98 ± 0.14</td>
<td>14.34 ± 1.76</td>
<td>16.6 ± 2.58</td>
<td>Jones et al (1997)</td>
</tr>
<tr>
<td>12</td>
<td>1.13 ± 0.66</td>
<td>10.29 ± 4.99</td>
<td>16.79 ± 5.07</td>
<td>Jaruratanasirikul &amp; Sriwiriyajan</td>
</tr>
<tr>
<td>P²</td>
<td>&lt; 0.001*</td>
<td>0.013*</td>
<td>&lt; 0.001*</td>
<td></td>
</tr>
<tr>
<td>Surgical Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>1.33 ± 0.30</td>
<td>11.4 ± 3.6</td>
<td>20.7 ± 5.4</td>
<td>Lovering et al (1995)</td>
</tr>
<tr>
<td>P³</td>
<td>0.021*</td>
<td>0.026*</td>
<td>0.001*</td>
<td></td>
</tr>
<tr>
<td>Critically Ill patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>2.4 ± 0.7</td>
<td>9.4 ± 1.2</td>
<td>26.6 ± 3.2</td>
<td>Thalhammer et al (1999)</td>
</tr>
<tr>
<td>8</td>
<td>2.5 ± 1.2</td>
<td>9.35 ± 2.43</td>
<td>21.7 ± 5.7</td>
<td>Kitzes-Cohen et al (2002)</td>
</tr>
<tr>
<td>10</td>
<td>2.13 ± 0.57</td>
<td>11.46 ± 3.13</td>
<td>27.1 ± 7.7</td>
<td>Novelli et al (2005)</td>
</tr>
<tr>
<td>P⁴</td>
<td>0.883</td>
<td>&lt; 0.001*</td>
<td>&lt; 0.001*</td>
<td></td>
</tr>
</tbody>
</table>

Table 4.9 Pharmacokinetic parameters from this study compared with published values (no renal impairment).

P¹ Lin burns study compared with this study.  P² difference between studies for healthy volunteers and this study.  P³ Surgical patients compared with this study.  P⁴ difference between studies for critically ill patients and this study.

** This figure was not stated in the paper, but was calculated from other data given in the paper.
The volume of distribution, clearance and half-life values were all significantly
greater in this study when compared with those of healthy volunteers (Bax et al.
1989; Kelly, Hutchison and Haworth 1995; Jones et al. 1997; Jaruratanasirikul and
Sriwiriyajan 2003). The mean clearance and volume of distribution were all
significantly greater in this study of burns patients when compared with these
parameters in other patients, including another study of the pharmacokinetics of
meropenem in patients with burns (Lin et al. 2004). The mean half-life in this study
was not significantly different from the means published for the burns study in
Chinese patients (Lin et al. 2004), or from critically ill patients (Thalhammer et al.
1999; Kitzes-Cohen et al. 2002; Novelli et al. 2005), but was significantly longer
than those for surgical patients (Lovering et al. 1995).

It can be seen that both the mean clearance and volume of distribution in this study
were larger than for any other study, but that the elimination half life was similar to
values for the other burns study and for critically ill patients without burns.

As six of the eight surgical patients in the study by Lovering et al (1995) were over
the age of 60, pharmacokinetic parameters of these six patients were compared
with the three patients in the current study who were over sixty years (Table
4.10). Because of the low numbers, the mean values were not compared
statistically, but it can be seen that the mean half-life and volume of distribution at
steady-state were still notably greater in this burns study, but there was less of a
difference between the two mean values for clearance.
<table>
<thead>
<tr>
<th>Study Group</th>
<th>Age (y)</th>
<th>t½ (hr)</th>
<th>Cl L/hr</th>
<th>Vdss (L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical (n=6)</td>
<td>70.8 ± 7.0</td>
<td>1.4 ± 0.3</td>
<td>11.2 ± 4.5</td>
<td>21.4 ± 6.6</td>
</tr>
<tr>
<td>Burns (n=3)</td>
<td>68.3 ± 5.7</td>
<td>3.6 ± 0.8</td>
<td>14.3 ± 7.5</td>
<td>40.3 ± 12.0</td>
</tr>
</tbody>
</table>

Table 4.10 Patients over the age of 60: Comparison of pharmacokinetic parameters of patients infected surgical patients (Lovering et al. 1995) with patients in this study.

The two groups were not compared statistically due to the low numbers of patients.

Seven of the twelve patients in this study required a higher dose than the standard 1g eight-hourly. This was predicted to be as high as 6g in 24 hours for some patients (Table 4.11). If a daily dose of 6g were administered as a continuous infusion, a T>MIC of 100% is predicted for all patients. A lower mean T>MIC of 84% is predicted for a bolus dose of 1g every four hours (range 48 to 100%), which is similar to a mean of 85% for eight-hourly 2g intermittent infusion over three hours at steady state. However, the range for the latter regimen was higher (57 to 100%). Administering the dose as a bolus of 2g every eight hours is predicted to result in the lower mean T>MIC of 72% (range 41 to 100%).

Administering a total daily dose of 6g as a 2g bolus dose every eight hours, is predicted to result in higher peak and lower trough concentrations (mean 51.0mg/L and 4.8mg/L respectively), than giving a bolus dose of 1g every 4 hours (mean 32.2mg/L and 9.6mg/L) (Table 4.12).
<table>
<thead>
<tr>
<th>Patient number</th>
<th>Bolus</th>
<th>Intermittent Infusion over 3 hrs</th>
<th>Continuous Infusion (SS)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1g 4-hourly (SS)</td>
<td>2g 8-hourly (SS)</td>
<td>1g 8-hourly (FD)</td>
</tr>
<tr>
<td>1</td>
<td>84</td>
<td>70</td>
<td>46</td>
</tr>
<tr>
<td>2</td>
<td>87</td>
<td>66</td>
<td>52</td>
</tr>
<tr>
<td>3</td>
<td>100</td>
<td>100</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>100</td>
<td>100</td>
<td>93</td>
</tr>
<tr>
<td>5</td>
<td>64</td>
<td>58</td>
<td>31</td>
</tr>
<tr>
<td>6</td>
<td>48</td>
<td>41</td>
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</tr>
<tr>
<td>7</td>
<td>77</td>
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<tr>
<td>11</td>
<td>100</td>
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</tr>
<tr>
<td>12</td>
<td>95</td>
<td>70</td>
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</tr>
<tr>
<td>Mean</td>
<td>84</td>
<td>72</td>
<td>62</td>
</tr>
<tr>
<td>S.D.</td>
<td>19</td>
<td>24</td>
<td>25</td>
</tr>
</tbody>
</table>

*Table 4.11 Predicted time (as a percentage of the dose interval) above 4mg/L for various dosing regimens*

FD = First dose, SS = steady-state. Predictions are based on pharmacokinetic data calculated from the first set of samples collected for each patient. See Appendix 9 for how these were calculated.
### Table 4.12 Predicted serum concentrations (mg/L) for differing dosing regimens

FD First dose, SS Steady-state. See Appendix 9 for how these were calculated.
4.4.5. Factors influencing pharmacokinetic profile

The patient factors and pharmacokinetic parameters for patients who did not require a dose increase from 1g eight-hourly (Group A) were compared with those who did (Group B) (Table 4.13).

The mean age of patients in Group A was higher than those in Group B ($p = 0.010$). Whilst there was a tendency of patients in group A to have a smaller size of burn and smaller size of full-thickness burn, the difference was not significant ($p = 0.066$ and $p = 0.157$ respectively). Similarly whilst the mean value for the day of sampling was lower in Group A patients, the difference was not significant ($p = 0.148$).

Although Group A patients had a higher mean serum creatinine and lower measured mean creatinine clearance, these differences were not significant. However when the creatinine clearance was calculated using the Cockcroft and Gault equation (Cockcroft and Gault 1976), the mean value was significantly lower for patients in Group A ($p = 0.033$). There was no significant difference between the mean albumin values for the groups.

Meropenem clearance mean values were significantly lower ($p = 0.008$), and the half-lives significantly longer ($p = 0.014$) in the patients who were managed using conventional dosing (Group A). Whilst there was a tendency towards smaller volumes of distribution when expressed in litres in this group, this did not not reach significance. Group A patients did, however, have a lower mean volume of distribution when is was calculated in L/kg ($p = 0.03$).
### Table 4.13 Patient factors and pharmacokinetic parameters according to dose required.

Patients who required a dose increase had significantly lower mean values for age and elimination half-life, and significantly higher mean values for estimated creatinine clearance, volume of distribution (in L/kg) and clearance. The values used were the ones that applied to the first set of samples taken.

$t\frac{1}{2} =$ elimination half-life, $V =$ volume of distribution, $\text{Cl} =$ total clearance
Age most strongly correlated with pharmacokinetic values (Figures 6.5a and b). It was positively associated with half-life ($r^2 = 0.746, p<0.001$), so that the older the patient, the longer the half-life. There was also a weaker negative correlation between age and meropenem clearance ($r^2 = 0.533, p = 0.007$) so that as age increased, clearance decreased.

**Figure 4.5a Relationship between age and meropenem half-life**
As age increased, so did the half-life or meropenem (p < 0.001).

**Figure 4.5b Relationship between age and meropenem clearance**
As age increased, meropenem clearance decreased (p = 0.007).
Additionally there were weaker correlations between the size of burn and meropenem clearance (positive correlation, $r^2 = 0.391$, $p = 0.029$), albumin with half-life (negative correlation, $r^2 = 0.209$, $p = 0.05$), the natural log of the half-life (negative correlation, $r^2 = 0.326$, $p = 0.016$) and volume of distribution (negative correlation, $r^2 = 0.288$, $p = 0.017$). No correlation was seen between any of the measures of renal function (serum creatinine, measured creatinine clearance and creatinine clearance as estimated by the Cockcroft and Gault Equation (Cockcroft and Gault 1976)) and pharmacokinetic values.

4.5. Discussion

This is the only study to investigate the influence of patient factors on both pharmacokinetic values and dosage requirements of meropenem in patients with burns, with the aim of proposing a dose regimen for this population. It has confirmed the hypothesis that patients with large burns have altered meropenem pharmacokinetics compared with non-burn populations, and that higher or more frequent dosing is required in some patients. As seen with many other studies of drugs in burns patients (Blanchet et al. 2008), there was large interpatient variation in the pharmacokinetics. Patient factors such as age and renal function may be factors when predicting the dosage requirements.

Curve fitting could not be undertaken as an insufficient number of samples were taken during the distribution phase, particularly as the first sample was not taken until 30 minutes after the start of the dose. This may have been as much as two distribution half-lives for some patients (Lin et al. 2004). If more samples had been taken earlier post-dose, pharmacokinetic parameters could have been calculated in the distribution phase. The relatively small number of samples per patient was chosen as it was sufficient to calculate pharmacokinetic parameters based on the elimination phase, and to achieve the aim of developing dosage guidelines, but kept the volume of blood required to a minimum (18ml per set of samples). This is particularly important in patients with burns, as they are generally anaemic, they are likely to have significant blood losses on their numerous visits to theatre, and
already have blood taken regularly for routine monitoring. Although curve fitting was not possible, visual inspection of the meropenem serum concentration vs time plot indicated that pharmacokinetics of meropenem in this study appeared to best fit a two-compartment model. This is in line with other studies of meropenem (Bedikian et al. 1994; Kelly, Hutchison and Haworth 1995; Lovering et al. 1995). However the distribution phase appeared to be longer than in studies with healthy volunteers (Drusano and Hutchison 1995), which is likely to be due to the increase in extra-vascular fluid which occurs with large burns.

In this burns study, the positive correlation between serum creatinine and age would be expected as it is well documented (in non-burn patients) that after the age of 40 years serum creatinine concentrations increase (Tiao et al. 2002). Whilst the use of the Cockcroft and Gault (C&G) equation (Cockcroft and Gault 1976) has been shown not be an accurate predictor of actual creatinine clearance in patients with major burns (Conil et al. 2007b), there is a linear relationship between the two ($R^2 = 0.3053$, $p < 0.0005$). Therefore the negative correlation between creatinine clearance (as estimated by the C&G equation) would also be expected.

More surprisingly is the negative correlation between age and size of burn ($r^2 = 0.3998$, $p = 0.003$). This may be related to early decisions regarding the path of treatment, as end of life care may be agreed upon for older patients who sustain large percentage burns, due to their extremely poor prognosis. Such patients would be unlikely to receive treatment with meropenem.

4.5.1. **Comparison with other pharmacokinetic studies of meropenem**

The mean volume of distribution in the current study was significantly larger than that measured in non-burn subjects and in one other study of patients with burns (Table 4.9). As discussed in Chapter 1, Section 1.7.3, a larger volume of distribution would be expected in patients with large burns due to the greater amounts of extracellular fluid. Therefore more of the antibiotic would be taken up into the tissues, leaving a lower concentration in the plasma compartment. A
greater clearance can also be predicted because of the hypermetabolic state of patient with burns increasing their cardiac output and therefore resulting in a greater blood flow through the kidney.

One might have expected the half-life of meropenem to be shorter in patients with major burns than healthy subjects, due to the increase in cardiac output as a result of the hypermetabolic response. Some studies have shown this to be the case with antibiotics such as the aminoglycosides (Sawchuk and Zaske 1976; Loirat et al. 1978; Zaske, Sawchuk and Strate 1978) and vancomycin (Garrelts and Peterie 1988). However, other studies have shown beta-lactams to have longer half-lives in burns patients (Walstad, Aanderud and Thurmann-Nielsen 1988; Shikuma et al. 1990). This is thought to be because the antibiotic is taking a longer time to redistribute from the tissues back into the intravascular compartment which is necessary before it can be excreted through the kidney (Blanchet et al. 2008).

The volume of distribution, clearance and half-life were all significantly greater in burned patients in this study compared with surgical patients with moderate or severe infections in other studies (Lovering et al. 1995), although their differences were less significant than those published for healthy subjects. Although eleven patients were recruited to the study, only eight had serum concentrations measured at steady-state. Lovering et al (1995) found that whilst no dosage modifications were required for their surgical patients, total clearances were closer to those published for healthy older men (Ljungberg and Nilsson-Ehle 1992) than for those published for younger healthy subjects (Bax et al. 1989). This was likely to be due to a mean age of 60 years in the eight patients in the study of meropenem steady-state pharmacokinetics in surgical patients (Lovering et al. 1995), with only two patients being under 60 years. Therefore any increases in clearance due to acute infection, may have been counteracted by the decline in renal function associated with increasing age (mean creatinine clearance of the patients over 60 years on day 4/5 was 66ml/min ± 19 compared with 107ml/min and 127ml/min for the two patients under 60 years). As the mean age of patients in this burns study was 46 years, it may not be appropriate to compare the two
groups. However when comparing the data for patients in each study who were over the age of 60 (Table 4.10), it can be seen that the clearance of meropenem for this age group was only slightly greater in this burns study than for surgical patients. This may be due to a lesser hypermetabolic response to burn injury in older patients, and therefore less of an increase in cardiac output and renal blood flow (personal observation in researcher’s role as clinical pharmacist).

The mean half-life in this study of burns patients was similar to those published for critically ill patients with sepsis without burns (Thalhammer et al. 1999; Kitzes-Cohen et al. 2002; Novelli et al. 2005), but the mean volume of distribution and clearance were significantly greater. The mean volumes of distribution in the critically ill patients were notably larger than those of healthy volunteers, which was probably due to increased capillary permeability and additional fluid outside the intravascular compartment, as occurs – but to a greater extent – in patients with major burns. This explains why the mean volumes of distribution and clearances are significantly larger in burns patients than critically ill patients without burns.

In 2004, a Chinese study (Lin et al. 2004) investigated the pharmacokinetics of meropenem in patients with severe burns and published some interesting findings. Unlike the current study where meropenem parameters were measured at steady state, these measured following a single dose. Pharmacokinetic parameters were calculated for 28 patients with TBSA burn ranging from 45 to 98%, following a single dose of meropenem 500mg (half of the dose given in the current study) given over 30 minutes. Whilst they measured a similar half-life to patients in this burns study, their reported volume of distribution, Vc, was the smallest of all of the studies reviewed here (10.60L ± 3.93). The authors noted that just after the intravenous injection, the mean plasma concentration of their burn patients (36.37 ± 10.51mg/L at 30 minutes) was significantly higher than that reported in a study of six healthy subjects (21.1 ± 10.7mg/L) (Leroy et al. 1992). Cmax in the current burns study (25.02 ± 11.23mg/L for the dose of 1g eight-hourly (Table 4.8) was lower than that reported by Lin et al (2004), despite the dose being double (dose and peak concentration are proportional if administered over the same time and
dose interval) and given over only 5 minutes. As the pharmacokinetics were calculated from serum samples taken at steady-state in the current study, it would be expected to give a larger peak serum concentration for the same dose.

There are generally three measures of volume of distribution referred to in the literature. $V_c$ is used in a two-compartment model and is a proportionality constant that relates the amount of the antibiotic with the immediate plasma concentration following its administration, i.e. only allows time for the meropenem to reach the highly perfused tissues such as the liver. Other measures of volume of distribution such as the volume at steady-state, i.e. allowing time to reach all tissues, would be expected to be higher.

From other data reported by Lin et al (2004), it was possible to calculate the mean of another measure of volume of distribution, the volume of distribution at steady-state, $V_{dss}$. This was 20.75L ± 5.35, which was comparable with $V_{dss}$ for other critically ill patients, but much smaller than the third measure, $V_{area}$ (or $V_β$ or $V_z$), the volume of distribution of 55.65L ± 27.31 calculated in the current burns study. $V_{area}$ relates to the plasma concentration and amount of the drug in the body in the elimination phase, once distribution equilibrium has been attained. This is likely to have led to an overestimation of the true volume of distribution because the drug has multicompartmental characteristics, and therefore may in part explain why the volume of distribution in the current study was larger.

Another possible reason for the smaller mean volume of distribution of meropenem in the study Lin et al (2004) compared with the current study, is how long after the burn was sustained that samples were taken. The text in this paper is Chinese, but it appears that meropenem samples were a mean of 3.7 ± 2.54 days after the injury in the former study, compared with 30 ±18 days in the current study. Whilst most of the patients should have been in the hypermetabolic phase by 3.7 days some of the patients would probably have been in the acute phase when samples were taken. Additionally it is possible that, even at 3.7 days, the full effect of volume changes which occur with a major burn may not have taken place.
Additionally all of the patients in the current study were being administered meropenem to treat sepsis, whereas it does not appear that the patients had sepsis in the single-dose study by Lin et al (2004). Sepsis is known to cause an increase in fluid volume of the body and hence an increase in the volume of distribution of drugs in critically ill patients without burns (Buerger et al. 2006). A final reason for the difference in the volume of distribution in the two studies may have been due to bodyweight differences. These were not stated for the study by Lin et al (2004), so it was not possible to compare the volume of distribution per kilogram of bodyweight.

In the same study, Lin et al (2004) also measured meropenem concentration in the urine and found that the recovery of the drug in their patients was 58%, which was much lower than the authors 75% quoted for healthy subjects. The authors suggested that this was due to a loss through the wound exudate. This proposal was supporting by their report in two patients of higher concentrations in the blister fluid than in plasma (data not given).

4.5.2. Influences of other factors on the pharmacokinetics of meropenem in patients with major burns

Exploring the data further from only the current burns pharmacokinetic study, it can be seen that there was marked inter-patient variability with the serum concentrations measured from the starting dose of 1g three times a day (Figure 4.4). Also, the percentage of the dose interval above 4mg/L at this dose ranged from 15% to 100%. This indicates that there are other factors affecting the pharmacokinetics, which is consistent with the Lin et al (2004) burns study and other studies of antibiotics in burns patients (Blanchet et al. 2008). Additionally, intra-patient variation was apparent, which may have been due to changes in renal function, fluid changes or time post-burn.

The differences in the pharmacokinetic parameters of meropenem in the study patients are most likely to be due to age and possibly renal function. Whilst the
means of both of these factors were significantly different in patients who required a dose increase and those who did not, it was surprising that there was no significant correlation between estimated creatinine clearance and any of the pharmacokinetic parameters. This may have been because of the use of the Cockcroft and Gault equation (Cockcroft and Gault 1976) to estimate creatinine clearance instead of measuring it directly, rather than measuring it from from a urine and blood collection. It was noticeable that the four oldest patients (59 years and older) all had therapeutic serum concentrations of meropenem at the standard dose, but only one of the other patients (Patient 12) did not require a dose increase. Samples in Patient 12 just reached 40% of the dose interval above 4mg/L, whereas the four oldest patients had serum concentrations well in excess of this. Additionally, samples for Patient 12 were taken only 5 days post-burn compared with at least 13 days for all of the other patients. At day five he had creatinine clearance of 215ml/min, an indication that he was hypermetabolic, but fluid changes may not have reached a maximum as indicated by his volume of distribution being lower than the average (0.57L/kg vs 0.69L/kg for the mean). This fits with one explanation for the lower mean volume of distribution of meropenem in the study by Lin et al (2004) compared with this study as discussed in Section 4.5.1.

A review of the literature of factors that may affect meropenem dosing in non-burn patients was undertaken. Christensson et al (1992) determined a linear correlation between the glomerular filtration rate (GFR) and meropenem clearance. The half-life of meropenem was longer in the patients with lower GFRs, but there were no differences in the volumes of distribution. The Summary of Product Characteristics for meropenem (AstraZeneca 2010) recommends a dose reduction in renal impairment i.e. creatinine clearances of less than 51ml/min. Ljungberg and Nilsson-Ehle (1992) found a significant reduction in the renal excretion rate of meropenem in older healthy volunteers compared with younger ones, which corresponded with the decline in renal function. However, they also found a decrease in non-renal clearance, thought to be due to a slower metabolism of meropenem.
The effect of patient factors has been considered with other antibiotics in burns patients. Boucher et al (1990) studied the pharmacokinetics of imipenem in burns ranging from 13 to 82% TBSA and found no statistically significant differences in any of the pharmacokinetic parameters compared with data published for healthy volunteers. There was however, a significant relationship between imipenem clearance and creatinine clearance, and the elimination rate constant and creatinine clearance. There was no relationship between imipenem clearance and total body surface area burn. They concluded that an adjustment in either dose or dose interval may be necessary in patients with very high or low creatinine clearances. Patients in the Boucher et al study (1990) ranged in age from 23 to 59 years (mean 36 years), much younger than in this current burns study, and the effect of age on the pharmacokinetics was not investigated.

Zaske et al (1991) studied the pharmacokinetics of gentamicin in 99 patients with burns ranging from 12 to 90% TBSA, with an age range of 1 to 86 years. They found that the elimination of gentamicin was significantly related to renal function estimates, despite using the Cockcroft and Gault equation to calculate creatinine clearance. Changes in creatinine clearance did not account for all of the variance in drug clearance, as age and hydration status were other factors. The volume of distribution, related to the extracellular fluid compartment, was an additional factor in explaining the half-life and elimination rate. The authors proposed a dosing schedule for patients with normal serum creatinine concentrations (≤ 132μmol/L) of giving higher total daily doses and more frequent dose intervals in younger patients. The effect of the total percentage burn surface area on gentamicin dosage was not reported.

Conil et al (1994) determined whether there were any correlations between vancomycin by continuous infusion and burn parameters, age and renal function in 18 patients with a mean TBSA of 40%. They concluded that higher initial doses of vancomycin were required in patients under the age of 60 years. More recently, Dailly et al (2008) proposed a formula to calculate the dose of vancomycin required
in patients with large burns, which was directly proportional to creatinine clearance. They did not investigate the influence of any other factors.

From the literature available, and the findings of this study, it seems likely that the dose of meropenem required is most dependent on age and/or on creatinine clearance. In patients with major burns, the same doses as non-burn patients may be sufficient in older patients or those without abnormally high creatinine clearances.

4.5.3. Pharmacokinetic and pharmacodynamic studies of meropenem from 2002 to 2010 – a review of the literature

Before proposing a dosing schedule, it should be determined whether the marker of efficacy selected for this study, should still be adopted. It was noticeable that of the five patients who did not survive their injury, three had therapeutic serum concentrations at the starting dose of 1 g every eight hours. In most, if not all cases, the cause of death was likely to be sepsis. This could have been due to the patients’ own abilities to fight sepsis, but it may have been because the target of 40% of the dose interval above 4 mg/L was insufficient. Therefore a review of the literature from 2002 was undertaken.

Whilst most studies up to 2002 indicated that 1 x MIC should be the target concentration for meropenem, one in vitro study has since suggested that a higher concentration may be required (Tam et al. 2005a). Using time-kill studies at escalating concentrations of meropenem against P. aeruginosa at a baseline of $10^8$ cfu/ml, a significant drop in bacterial burden was seen at 24 hours with concentrations at 4 x MIC. With a concentration of 1 x MIC a drop in the cfu/ml was seen up until 4 hours, but regrowth was noted at 12 to 24 hours. The authors concluded that meropenem exhibited a partially concentration-dependent killing profile. This has previously been reported in vitro with both cefepime (Tam et al. 2002) and meropenem (Bowker et al. 1996). It should be noted that the experiment by Tam et al (2005a) was conducted over 24 hours at a temperature of 25°C, when significant degradation of meropenem would be expected. As a
second part to the study, a growth dynamics model was used to calculate the concentrations of meropenem required to achieve an 80% and 90% maximal kill rate. These concentrations were 3.8 and 5.0 mg/L respectively. Whilst this study does not provide sufficient evidence to aim for a multiple of the MIC, it should be noted that with an intermittent dosing schedule, meropenem peak concentrations are well in excess of likely MICs, but this may not be the case with administration by continuous infusion.

The MIC selected for the current study was 4mg/L for reasons already outlined in section 4.3. In 2007, in order to standardise breakpoints across Europe, the British Society of Antimicrobial Chemotherapy altered some breakpoints, with some being reduced to a MIC of 2mg/L or less. Intermediate sensitivity became 4 to 8mg/L, and “resistant” became an MIC of greater than 8mg/L (BSAC 2007). The work was undertaken by the European Committee on Antimicrobial Sensitivity Testing (EUCAST), which included a review of the current data on pharmacodynamics of antibiotics, as well as susceptibility distributions, resistance mechanisms, and clinical outcomes relating to *in vitro* tests. Current British Society for Antimicrobial Chemotherapy Guidance (BSAC 2010) states the susceptibility breakpoints to be 2mg/L for all organisms. For the majority of pathogens intermediate susceptibility is listed as 4 to 8mg/L and with the resistant breakpoint being greater than 8mg/L.

This may lead to the proposal that the target concentration of meropenem should be 2mg/L. However, a recent study activity of meropenem against nosocomial isolates across Europe (Turner 2009) showed that whilst some common burns pathogens had an MIC$_{90}$ of less than 2mg/L, this figure was 6mg/L for *Acinetobacter* spp. and 16mg/L for *Pseudomonas aeruginosa* (Table 4.14). The percentage susceptible at a breakpoint of 4mg/L was over 80% for organisms other than for these two (74% and 79% respectively). It could be proposed that instead of using a single target concentration, the MICs should be measured, as is now possible. However, meropenem is often used as empiric therapy, and therefore the infecting organism may not be isolated until after treatment has commenced, if ever. A meropenem serum concentration of 4mg/L would therefore seem a
reasonable target to continue with for empiric therapy regimens. Where the MICs are known, the minimum concentration should remain as 4mg/L as there may be pathogens that are not isolated in culture. However if the MIC$_{90}$ is higher than 4mg/L, the target concentration may be increased accordingly depending on the clinical status of the patient.

<table>
<thead>
<tr>
<th></th>
<th>MIC (mg/L) range</th>
<th>MIC$_{90}$ (mg/L)</th>
<th>% susceptible at breakpoint of 4mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gram positive</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Bacillus cereus</em></td>
<td>0.012 - 32</td>
<td>32</td>
<td>86</td>
</tr>
<tr>
<td>Coagulase negative staph.</td>
<td>$\leq 0.008 - 64$</td>
<td>8</td>
<td>89</td>
</tr>
<tr>
<td><em>Enterococcus faecalis</em></td>
<td>$&lt; 0.008 - 64$</td>
<td>16</td>
<td>-</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>$\leq 0.008 - 4$</td>
<td>0.25</td>
<td>100</td>
</tr>
<tr>
<td><strong>Gram negative</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Acinetobacter spp</em></td>
<td>$&lt; 0.008 - 128$</td>
<td>6</td>
<td>74</td>
</tr>
<tr>
<td><em>Enterobacter spp</em></td>
<td>$&lt; 0.008 - &gt;128$</td>
<td>0.13</td>
<td>99</td>
</tr>
<tr>
<td><em>Klebsiella spp</em></td>
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<td>0.06</td>
<td>99</td>
</tr>
<tr>
<td><em>Proteus mirabilis</em></td>
<td>$\leq 0.008 - 2$</td>
<td>0.13</td>
<td>100</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>$&lt; 0.008 - 128$</td>
<td>16</td>
<td>79</td>
</tr>
</tbody>
</table>

Table 4.14 Susceptibility reports of common burns pathogens to meropenem adapted from Turner (2009)

* Includes *E.Coli*, and *E. Cloacae*

Whilst the BSAC breakpoint for meropenem is now 2mg/L, several organisms that are common pathogens in patients with burns have an MIC$_{90}$ higher than this. It is therefore appropriate to continue with a target concentration for empiric therapy to be 4mg/L.

Studies continue to be inconclusive as to what proportion of the dose interval is required to be above the MIC. Some indicate maximum efficacy is not achieved at 40% (Table 4.15).
<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
<th>Antibiotic(s)</th>
<th>Organism(s)</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ariano et al (2005)</td>
<td>60 febrile neutropenic patients</td>
<td>Meropenem</td>
<td>Gram positive and negative organisms</td>
<td>Median T &gt; MIC was 83% for responders, and 59% for non-responders</td>
</tr>
<tr>
<td>Du et al (2006)</td>
<td>37 paediatric patients with meningitis</td>
<td>Meropenem</td>
<td>Mainly <em>H.influenzae</em></td>
<td>All causative pathogens were eradicated from the CSF. Patients had T &gt; MIC ratios of 72% to 100%.</td>
</tr>
<tr>
<td>DeRyke et al (2007)</td>
<td>Neutropenic mouse thigh model</td>
<td>Meropenem, Ertapenem</td>
<td><em>E.coli, K.pneumoniae</em></td>
<td>The standard dose of meropenem (T&gt;MIC 30 to 65%) had greater potency against organisms with higher MIC than the standard dose of ertapenem (T&gt; MIC less than 20%)</td>
</tr>
<tr>
<td>Li et al (2007)</td>
<td>101 Patient with lower respiratory tract infections</td>
<td>Meropenem</td>
<td>Gram positive and negative organisms</td>
<td>Cmin/MIC ratio of &gt; 5 best predictor, but also T&gt;MIC of &gt; 54%, and Cmax/MIC ratio of &gt; 383.</td>
</tr>
<tr>
<td>McKinnon, Paladino and Schentag (2008)</td>
<td>76 patient with serious bacterial infections</td>
<td>Cefepime and ceftazidime</td>
<td>Mainly Gram negative organisms</td>
<td>Outcome significantly greater when over T&gt; MIC was ≥ 80% and AUIC ≥ 125.</td>
</tr>
</tbody>
</table>

**Table 4.15 Studies to determine the marker of efficacy of beta-lactams**

MIC = Minimum inhibitory concentration, T>MIC = Percentage of the dose interval above the MIC, CSF = Cerebrospinal fluid, Cmin = Minimum (trough) concentration, Cmax = Maximum (peak) concentration. AUIC = Area under the inhibitory curve

Studies since 2002 suggest that concentrations should remain above the MIC for longer than 40% to achieve maximum efficacy.
DeRyke et al (2007) used the neutropenic mouse thigh model to study the bactericidal activities of meropenem and ertapenem against extended-spectrum-β-lactamase-producing E.coli and K.pneumoniae. Antibiotic dosing in the mice was designed to simulate concentrations seen in healthy adult humans at a dose of 1 g eight-hourly for meropenem and 50 mg/kg six-hourly for ertapenem. After 24 hours the mice were sacrificed and the bacterial counts were measured in the thigh. No difference in bacterial kill was seen with the two antibiotics for the organisms that had low MICs (≤ 0.5 mg/L for meropenem and ≤ 1.5 mg/L for ertapenem), which corresponded to a T > MIC of ≥ 75% for meropenem and ≥23% for ertapenem. For seven of the eight isolates where the MIC for ertapenem was ≥ 2 mg/L, a greater bacterial kill was seen in the mice treated with meropenem. This was thought to be due to the greater T>MIC of meropenem (30 to 65%) compared with ertapenem (≤ 20%).

Ariano et al (2005) studied sixty febrile neutropenic patients with confirmed bacteraemia. They compared the time above the MIC of responders to meropenem therapy (as defined by resolution of all signs and symptoms, continued stable signs on discontinuation of antimicrobial therapy and no further need for antibiotics for treatment of relapse) with non-responders. The median T>MIC for responders was 83%, but only 59% for the non-responders (p=0.04). The authors calculated that an 80% response rate was evident when concentrations remained above the MIC for at least 75% of the dose interval.

There are several limitations to the study by Ariano et al (2005). Firstly meropenem levels from serum samples of the individual patients were not measured, but instead, the investigators used a population-based predictive model based on pharmacokinetic data from a previous study of 12 febrile neutropenic patients (Nyhlen et al. 1997). Secondly the responders were younger than the non-responders (mean 34 years versus 46 years) and had lower mean MICs (0.13 vs 0.50) to the infective organisms. Also, over a half of the isolates were Staphylococcus epidermis, and only 15% were Gram-negative bacteria which
meropenem is most often used to treat. As there may be differences in the post-antibiotic effect of meropenem depending on the organism, this may be of relevance.

Du et al (2006) investigated the pharmacokinetics and pharmacodynamics of meropenem in paediatric patients. They used 425 blood samples from 99 patients to develop a population pharmacokinetic model. These data were then used to determine pharmacodynamic indices in relation to microbiological outcome (negative cerebrospinal fluid (CSF) cultures at the end of therapy or sterile cultures on a subsequent CSF analysis) in 37 patients with meningitis. As all causative organisms were eradicated from the CSF, they were unable to group the patients into responders and non-responders. The T>MIC ranged from 72 to 100%, which would indicate that serum concentrations do not need to be above the MIC for the entire dose interval.

Li et al (2007) used demographic data and a population pharmacokinetic model to link meropenem pharmacodynamic indices to the response in 101 patients with lower respiratory tract infections. Whilst a T>MIC of at least 54% was found to be a predictor of microbiological response, the most significant predictor of successful clinical (cure or improvement in all signs and symptoms and no additional antibiotic therapy required) and microbiological outcome (eradication or presumed eradication) was a minimum free drug concentration ($C_{\text{min}}$) to MIC ratio of greater than 5. Additionally a ratio of the maximum free drug concentration ($C_{\text{max}}$) to MIC ratio of greater than 383 was also a significant indicator of microbiological, but not clinical, response. The investigators highlight that 82% of patients had a T>MIC of 100% as the majority of MICs were less than 1mg/L. Therefore the sample size for patients with a $T > \text{MIC}$ of less than 100% was small. Also, of the 17 clinical and/or microbiological failures, eleven had serum concentrations above the MIC for 100% of the dose interval, again indicating that T>MIC may not be the only factor in determining infection outcome. The majority of patients in that study had nosocomial infections in the lower respiratory tract, which is also a common site of infection in burns patients.
McKinnon, Paladino and Schentag (2008) looked at the parameters of area under the inhibitory curve (AUIC) and T>MIC in relation to bacterial eradication and clinical cure with cefepime and ceftazidime. They concluded that these parameters were significantly better when the area under the inhibitory curve (AUIC) was ≥ 250 and the T>MIC was 100%. However, they also found very similar eradication rates and clinical cures when

- the AUIC was > 125 (95.5% / 79.1% bacteriological eradication / clinical cure for ≥ 250 vs 93.1% / 77.8% for ≥ 125) and when
- the T>MIC was over 80% (97% / 82.1% bacteriological eradication / clinical cure for T>MIC of 100% vs 95.6% / 82.6% for T>MIC of ≥ 80%).

As a previous study (1993) has indicated that cephalosporins require higher T>MIC than carbapenems for efficacy, the findings by McKinnon, Paladino and Schentag (2008) may not apply to other beta-lactam antibiotics such as meropenem.

Meropenem clinical studies applying pharmacodynamic principles continue to vary in their selected marker of efficacy, although all have used T>MIC and not multiples of MIC, $C_{\text{max}}$ or $C_{\text{min}}$ (Table 4.16). The most commonly selected target is T>MIC of 40%.

In summary, the marker of efficacy for meropenem continues to be thought to be related to serum concentrations. The majority of pharmacodynamic studies indicate that maximal efficacy is related to T>MIC, but also may be at least in part be related to a multiple of the MIC, or the peak or trough concentrations. Pharmacokinetic studies (Table 4.16) continue to use the percentage of the dose interval above the MIC as the marker of efficacy, with this figure varying from 20 to 100%, although most commonly 40% has been used.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Population</th>
<th>T&gt;MIC used</th>
<th>Dose recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaruratanasirikul and Sriwiniyajan (2003)</td>
<td>12 healthy volunteers to investigate 3 hour infusion</td>
<td>60%</td>
<td>3 hour intermittent infusion of 0.5g or 1g</td>
</tr>
<tr>
<td>Kuti et al (2003a)</td>
<td>Monte Carlo Simulation using data from healthy volunteers</td>
<td>30% and 50%</td>
<td>Up to 2g eight-hourly depending on the MIC of the infective organism</td>
</tr>
<tr>
<td>Kuti et al (2003b)</td>
<td>Monte Carlo Simulation using data from healthy volunteers</td>
<td>30% or higher</td>
<td>Doses as low as 500mg six-hourly may be effective</td>
</tr>
<tr>
<td>Maglio et al (2003)</td>
<td>10 healthy volunteers to determine concentrations in blister fluid</td>
<td>30%</td>
<td>500mg eight-hourly</td>
</tr>
<tr>
<td>Kuti et al (2004a)</td>
<td>Monte Carlo simulation</td>
<td>30%, 50% and 100%</td>
<td>None</td>
</tr>
<tr>
<td>Kuti et al (2004b)</td>
<td>7 volunteers with cystic fibrosis</td>
<td>100%</td>
<td>Continuous infusion of 125mg/hr (susceptible) or 250mg/hr (intermediately susceptible)</td>
</tr>
<tr>
<td>Kuti et al (2005)</td>
<td>Monte Carlo simulation using data from healthy subjects and patients</td>
<td>50%</td>
<td>None</td>
</tr>
<tr>
<td>Mikamo and Totsuka (2005)</td>
<td>Monte Carlo simulation using data from healthy volunteers</td>
<td>30% and 50%</td>
<td>1g eight-hourly</td>
</tr>
<tr>
<td>Novelli et al (2005)</td>
<td>10 critically ill patients with sepsis</td>
<td>40%</td>
<td>None</td>
</tr>
<tr>
<td>Kuti and Nicolau (2005)</td>
<td>Monte Carlo Simulation from patients on CVVH</td>
<td>40%</td>
<td>1g eight-hourly</td>
</tr>
<tr>
<td>Conte Jr et al (2005)</td>
<td>48 healthy adults to investigate intrapulmonary pharmacokinetics</td>
<td>40%</td>
<td>Eight-hourly administration</td>
</tr>
<tr>
<td>Lomaestro and Drusano (2005)</td>
<td>Monte Carlo Simulation using data from volunteers and patients</td>
<td>40%</td>
<td>1g given over three hours eight-hourly for organisms with high MICs</td>
</tr>
</tbody>
</table>

*Table 4.16 Pharmacokinetic studies of meropenem since 2002*
<table>
<thead>
<tr>
<th>Reference</th>
<th>Population</th>
<th>T&gt;MIC used</th>
<th>Dose recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaruratanasirikul, Sriwiniyajan and Punyo (2005)</td>
<td>9 patients with pneumonia</td>
<td>60%</td>
<td>Dose to be administered over 3 hours. 2g eight-hourly effective against pathogens with intermediate resistance.</td>
</tr>
<tr>
<td>Krueger et al (2005)</td>
<td>16 healthy volunteers to evaluate continuous infusion</td>
<td>40%</td>
<td>Continuous infusion</td>
</tr>
<tr>
<td>Lee et al (2006)</td>
<td>Monte Carlo Simulation using data from febrile neutropenic patients</td>
<td>40%</td>
<td>Doses of at least 1g eight-hourly</td>
</tr>
<tr>
<td>Li et al (2006a)</td>
<td>Monte Carlo Simulation using data from infected patients</td>
<td>20% and 40%</td>
<td>Administration over 3-hours</td>
</tr>
<tr>
<td>Santos Filho et al (2007)</td>
<td>Monte Carlo simulation</td>
<td>40%</td>
<td>2g, given over 3 hours, eight-hourly for pathogens with high MICs</td>
</tr>
<tr>
<td>Lodise et al (2007)</td>
<td>Monte Carlo simulation using data from 10 hospitalised patients</td>
<td>50% and 100%</td>
<td>None</td>
</tr>
<tr>
<td>Bradley et al (2008)</td>
<td>37 neonates</td>
<td>60%</td>
<td>20mg/kg eight-hourly</td>
</tr>
<tr>
<td>Cheatham et al (2008)</td>
<td>20 hospitalised patients</td>
<td>40% and 60%</td>
<td>500mg six-hourly sufficient against most pathogens</td>
</tr>
<tr>
<td>Langgartner et al (2008)</td>
<td>6 patients receiving continuous renal replacement therapy</td>
<td>100%</td>
<td>Continuous infusion may be effective</td>
</tr>
<tr>
<td>Roberts et al (2009)</td>
<td>Monte Carlo simulation of patients with sepsis</td>
<td>40%</td>
<td>Extended or continuous infusion of doses up to 6g/day may be more effective than bolus dosing for the treatment of less susceptible pathogens</td>
</tr>
<tr>
<td>Ikawa et al (2010)</td>
<td>Monte Carlo simulation in adult patients</td>
<td>40%</td>
<td>Low dose of 0.25g 12-hourly achieved a target attainment probability of over 80% for most organisms tested, but higher dose needed against P. aeruginosa.</td>
</tr>
</tbody>
</table>

Table 4.16 continued. Pharmacokinetic studies of meropenem since 2002

The marker of efficacy for studies ranges from a T>MIC of 20% to 100%. Most commonly 40% has been used. The Monte Carlo Simulation is a method used to evaluate the probability of experimental dosage regimens in attaining pre-specified pharmacodynamic targets against specific pathogens.
4.5.4. Meropenem dosing options for patients with major burns

Without being certain of the marker of efficacy, it is difficult to propose a dosing schedule. In the absence of any conclusive evidence, it may be appropriate to continue to aim for a minimum 40% of the dosing interval above 4mg/L. In this burns pharmacokinetic study, it appears that all patients would have achieved this goal if the standard starting dose had been a total daily dose of 6g in 24 hours, but for some, 3g in 24 hours was sufficient. Given the critically ill status of the major burns patient, it is therefore better to give higher doses than may be required, than to risk under-dosing, particularly as toxicity is unlikely to be a problem.

Dose adjustments in the current study were based on altering the frequency of dosing rather than changing the dose itself. Although, a bolus dose of 1g every four hours is likely to have resulted in serum concentrations in excess of 4mg/L for 40% of the dose interval for all of the patients in this burns study, administering the same total daily dose in a different way may have further increased the T>MIC (Table 4.11). This could allay concerns that the target T>MIC for maximal efficacy is higher than 40%.

As expected, a bolus dose of 2g every eight hours compared with 1g 4-hourly decreases both the mean predicted T>MIC (72% vs 84% at steady state), and the predicted T>MIC ranges (41 to 100%, vs 48 to 100%). With patient numbers 6 and 8, this may have actually resulted in a T>MIC of less than 40%, as the calculation is based on a non-compartmental model. Therefore the T>MIC calculated may be an over-estimate.

To extend T>MIC a dose can be administered as intermittent infusion, for example administration over three hours instead of a bolus over 5 minutes (Jaruratanasirikul and Sriwiriyajan 2003). In the current study the mean predicted T>MIC was higher for a dose of 2g when given over 3 hours every eight hours compared with when the same dose was given as a bolus (means 85% vs 72%). Similarly, a Monte Carlo simulation (Kuti et al. 2003a) showed that administering the same dose over
a longer period of time, was more likely to attain a bacteriostatic response against pathogens with higher MICs. Based on pharmacokinetic data from six healthy volunteers, Kuti et al (2003a) predicted that the target attainment rate for a bactericidal response (50% T>MIC) with meropenem against *P. aeruginosa* increased from 79.9% for 2g eight-hourly given over 30 minutes, to 84.0% when the same dose was given over 3 hours.

In the current study, the percentage of the dose interval above the MIC, and also predicted peak and trough serum concentrations were calculated for first doses of both 1g and 2g given over three hours (Tables 4.11 and 4.12). The predicted values indicate that a dose of 2g is required for some patients to achieve a T>MIC of over 40%, although at least nine patients would have achieved this at a dose of 1g over three hours. As it is thought that an early achievement of therapeutic antibiotic concentrations improve patient outcome, the higher dose is preferable to maximise the chances of therapeutic serum concentrations being achieved in all patients with major burns. At steady state, at least one patient would have had sub-therapeutic levels at the 1g dose. The 2g dose also results in higher peak and trough concentrations which may be beneficial if meropenem does have some degree of concentration-dependent killing.

Comparing the predictions for a regimen of a 1g bolus every four hours and a 2g infusion (over three hours) every eight hours, it can be seen that they result in very similar T>MICs of 84±19 and 85±15 respectively (ranges 61 to 100, and 63 to 100. The predicted peak and trough concentrations were also similar (mean 32.2/9.6 and 30.2/7.8mg/L). Whilst there are studies comparing the same dose regimen of beta-lactams given as either a bolus or an intermittent infusion, there are none comparing an intermittent infusion with a more frequent bolus dose schedule.

There are several papers supporting the use of a continuous infusion of beta-lactams and vancomycin, where the efficacy is related to the T > MIC (Mouton and Vinks 1996; Wysocki et al. 2001). This has an additional benefit if the activity of the antibiotic is related to the minimum serum concentration. A possible drawback
to this method of administration arises if the activity is related to peak serum concentrations, as these will be lower than with an intermittent dosing regimen.

A prospective cross-over study (Thalhammer et al. 1999) of continuous versus intermittent infusion administration of meropenem in critically ill patients with infection compared the pharmacokinetics of a 2g bolus (over 15 minutes) followed by an infusion of 3g/24 hours with an intermittent dosing schedule of 2g every eight hours. In both scenarios the serum concentrations were above the MIC for 100% of the time. In volunteers with cystic fibrosis (Kuti et al. 2004b), doses of 3g/24 hours and 6g/24 hours resulted in mean steady-state serum concentrations ($C_{ss}$) of 8.31 ± 0.68 mg/L and 18.50 ± 3.31 mg/L respectively. The authors suggest that the higher regimen may be necessary for pathogens reported as having intermediate sensitivity (8mg/L). Similarly, a study in patients undergoing continuous renal replacement therapy found that with the same total daily dose, the time the concentrations were above 4mg/L and 8mg/L were greater with the continuous infusion compared with intermittent infusion (Langgartner et al. 2008).

Krueger et al (2005) used the Monte Carlo simulation to evaluate the pharmacokinetics of intermittent administration and continuous infusion. They concluded that continuous administration of a dose of 3g over 24 hours was more likely to achieve the target attainment of at least 40% of the dose interval above the MIC of $P. aeruginosa$, than intermittent dosing and therefore should be used for both the treatment of infection due to this organism, as well as empirical therapy.

Several studies have demonstrated that continuous infusions of beta-lactams are at least as clinically effective as intermittent dosing with either the same total daily dose or a lower total daily dose for the continuous infusion (Grant et al. 2002; Lau et al. 2006; Van Zanten et al. 2007). Lorente et al (2006) compared the efficacy of continuous and intermittent infusion of meropenem. This retrospective study of 89 patients with ventilator-associated pneumonia (VAP) due to Gram-negative bacilli compared the clinical cure rates of the two meropenem regimens. Cure was defined as a complete resolution of all signs and symptoms of pneumonia. All
patients also received once-daily administration of tobramycin. A 90.5% clinical cure rate was recorded following continuous infusion of meropenem at a dose of 4g/24 hours, compared with only 59.6% with intermittent infusion (over 30 minutes) of 1g every six hours (p<0.001). There were no significant differences between the two groups in baseline characteristics, responsible microorganisms or their MICs. Differences were less significant for causative organisms with an MIC of 0.25 to 0.49mg/L (p=0.03) compared with an MIC of at least 0.5mg/L (p=0.003), probably because of the high cure in both groups in the VAP caused by the lower MICs. Serum concentrations were not reported. The authors concluded that administration of meropenem by continuous infusion may be more clinically effective that the same dose administered as an intermittent infusion, but that more studies were required to confirm this. There are no published reports of increased adverse effects with continuous infusion beta-lactams, including meropenem, compared with intermittent infusion.

In the current burns study, with a continuous infusion of meropenem of 6g in 24 hours, most patients are predicted to have achieved a steady-state concentration well in excess of 4mg/L. However, in three patients, the concentrations are predicted to have been less 8mg/L, with one being as low as 5.2mg/L. As shown in Table 4.14 some common burns pathogens may have MICs that are higher than the target of 4mg/L. Whilst a bolus dose would be given at the start of treatment, it could be three or more days before the serum concentrations of meropenem are known and a dose increase made, with the risk of sub-therapeutic treatment for the majority of this time. With an intermittent regimen, even with a dose as low as 1g eight-hourly, it is highly likely that the MIC would be exceeded for at least some of the dose interval.

Additionally there are two potential practical difficulties with continuous administration. Firstly, a dedicated intravenous line is needed. This can be a problem if there are Y-site (where two or more solutions of drugs are infused through the same line) incompatibilities with other antibiotics being administered continuously. However, in practice, this is only likely to be with vancomycin, which
meropenem does have Y-site compatibility with (Patel and Main 1996). The other potential problem is the stability of meropenem solution at room temperature. Meropenem, 1 to 20mg/L, is stable for up to 8 hours at 25°C in sodium chloride 0.9% solution, which would be the standard solution, and would not add to the workload of nursing staff compared with current practice. Occasionally patients with burns have a high sodium level. In such cases, meropenem would be given in a glucose solution, which has a stability of only 3 hours at 25°C (AstraZeneca 2007). This would mean frequent changes of infusion, which is additional work for nursing staff.

Continuous infusion of meropenem does offer the practical advantage that once steady state has been reached, only a single blood sample is required which can be taken at any time, compared with multiple blood samples at set times for the intermittent dosing regimens.

Whilst all of the methods of administration were predicted to achieve the minimum T>4mg/L of 40% in all of the patients with a total daily dose of 6g of meropenem, each method has its own advantages and disadvantages, which have previously been discussed. These are summarised in table 4.17.
<table>
<thead>
<tr>
<th>Consideration</th>
<th>Bolus 1g 4-hourly</th>
<th>Intermittent infusion 2g 8-hourly</th>
<th>Continuous infusion 6g/24 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence for use</td>
<td>Most evidence available.</td>
<td>Some evidence to indicate that better than bolus dosing.</td>
<td>Some evidence to indicate that better than 1g bolus dosing.</td>
</tr>
<tr>
<td>Licensed use</td>
<td>1g bolus dose licensed every eight hours</td>
<td>2g every eight hours licensed but only over 15 to 30 minutes.</td>
<td>No</td>
</tr>
<tr>
<td>T&gt;MIC</td>
<td>Not 100%</td>
<td>Not 100%</td>
<td>100%</td>
</tr>
<tr>
<td>Risk of not attaining target</td>
<td>Unlikely, but will always have a T&gt;MIC of more than 0% for sensitive organisms.</td>
<td>Unlikely, but will always have a T&gt;MIC of more than 0% for sensitive organisms.</td>
<td>Possible, and if so would be a T&gt;MIC of 0%</td>
</tr>
<tr>
<td>Peak concentration</td>
<td>Likely to be several times MIC</td>
<td>Likely to be several times MIC</td>
<td>May only be just in excess of MIC</td>
</tr>
<tr>
<td>Trough concentration</td>
<td>May be below MIC</td>
<td>May be below MIC</td>
<td>Likely to be in excess of MIC</td>
</tr>
<tr>
<td>Ease of administration</td>
<td>Easiest</td>
<td>Less easy than bolus</td>
<td>More difficult than intermittent infusion if needs to be given in a glucose solution.</td>
</tr>
<tr>
<td>Y-site compatibility</td>
<td>Unlikely to be a problem</td>
<td>Needs to be considered</td>
<td>Needs to be considered</td>
</tr>
<tr>
<td>Equipment</td>
<td>Only a syringe and needle</td>
<td>Syringe, syringe driver, needle and line</td>
<td>Syringe, syringe driver, needle and line</td>
</tr>
<tr>
<td>Ease of monitoring</td>
<td>May need to take only two samples (at 2 hours and pre-dose)</td>
<td>May need more samples than bolus dose due to slower time to reach MIC</td>
<td>Easiest as can take a single sample at any time, once infusion has reached steady state.</td>
</tr>
</tbody>
</table>

Table 4.17 Advantages and disadvantages of the different methods of administration of meropenem at a total daily dose of 6g.

As no method has shown a clear benefit in patient outcome, and continuous infusion has the potential risk of even 6g/24 hours resulting in a T>MIC of 0%, it would seem appropriate to opt for either a bolus or an intermittent infusion of meropenem. These methods may also be clinically more effective if there is an element of concentration-dependent killing. Bolus dosing offers the advantages over an intermittent infusion of simpler administration, avoids the risk of Y-site incompatability and a saving on the equipment required. The dose should be 1g every four hours, although less frequent dose intervals could be considered in
older patients without abnormally high creatinine clearance rates. Increasing the administration time from five to thirty minutes may maximise the time above the target concentration, and is in line with the recommendations of the manufacturer's license. With this regimen peak concentrations are predicted to be in excess of the intermediate breakpoint of 8mg, and the percentage of the dose interval above 4mg/L should be over 40% in all cases. Even if this is not the case, values would still be well above 0%. Higher doses may be required where MICs above 4mg/L are recorded.

As this study was limited to 12 patients, the monitoring of serum concentrations should continue for all new patients commencing treatment with meropenem, in order to confirm the effectiveness of the dosing recommendations made. The number of samples could be reduced to two; one at two hours post dose, after the completion of the distribution phase, and the other immediately before the next dose. This would be sufficient to calculate the pharmacokinetics in the elimination phase and to adjust doses accordingly. Steady state is reached after 4.32 half-lives (Jambhekar and Breen 2009). With the twelve study patients, the longest half life recorded was four hours, so samples could be taken from twenty-four hours after the commencement of treatment.

4.6. Conclusion

This study of twelve patients with major burns who were treated with meropenem for the control of microbial infections has demonstrated that the pharmacokinetics of meropenem were altered when compared with those in both healthy volunteers and other patient populations. Despite the problem of a wide inter-patient variability, it is necessary to develop a dosing regimen that is likely to be effective in the treatment of otherwise life-threatening infections in patients with severe burns.
There were several limitations to this study, in addition to the ones already outlined. As this was a study on real patients where the clinical staff were recording information there were unfortunately some omissions in the records. A retrospective search through each patient’s notes highlighted some short-comings. Sometimes this was because some parameters were never measured such as creatinine clearance values and the heights of patients, or just not recorded in the notes such as the percentage burn remaining at the time of sampling. Others were due to missing medical notes.

In most cases, blood samples were collected at the planned times, as directed on the pre-printed sheet (Appendix 6). There were two occasions where the nursing staff gave the dose of meropenem before the pre-dose sample was taken. Similarly two post-doses blood samples were missed; one due to a problem taking the blood, and one where the following dose of meropenem was given two hours early in error.

The statistical analysis selected for comparing burns patients in this study with other studies could be criticised, as ideally the data should be compared with other treatment groups in the same study. This is because there may have been other differences in the study populations e.g. different renal function or mean age. Where known, the differences have been highlighted such as in the study of meropenem in surgical patients by Lovering et al (1995) in Section 4.5.1.

The pharmacokinetic parameters calculated for this study were used to predict peak and trough serum concentrations and the T>MIC for each patient for different dosing regimens. These indicated that if a single standard dose were to be recommended for all patients with severe burns, it would be a total daily dose of 6g in 24 hours. This applied whether the meropenem was to be administered as a bolus dose, an intermittent infusion or a continuous infusion. However for some patients a total daily dose of 3g in 24 hours would have been sufficient. Combining this data with a review of the literature led to the conclusion that patients with burns
who do not require doses as high as 6g in 24 hours were likely to be those who were older or did not have abnormally high creatinine clearances.

The evidence for the marker of efficacy selected for this study (a concentration above 4mg/L for at least 40% of the dose interval) was reviewed. There is still no clear consensus on what marker should be used, and whilst it is still thought that meropenem’s effect is predominantly time-dependent, there may also be an element of concentration dependent killing. Evidence suggests that although the most effective method of administration of meropenem may be as a continuous intravenous infusion, in patients with severe burns there is a risk that administration by this method, even at doses as high as 6g in 24 hours, could result in the MIC never being achieved during the whole dosing interval. There was little difference in the predicted percentage time above the dose interval and in peak and trough serum concentrations between a dose of 1g bolus every four hours, and an intermittent infusion of 2g over three hours every eight hours. Bolus administration was selected as it offered practical and cost advantages over intermittent infusion, making this the recommended method of administration.

4.7. Recommendations

A meropenem bolus dose of 1g every four hours should be administered as the standard dose in patients with severe burns. Lower doses may be effective in older patients or those without evidence of abnormally high creatinine clearance measurements. Higher doses may be required where MICs above 4mg/L are recorded. Serum concentration monitoring should continue, but at a reduced frequency of being taken two hours after the start of the dose and then immediately before the next dose. These may be taken from 24 hours after the start of treatment. Doses should be adjusted to achieve serum concentrations of a minimum of 40% of the dosing interval above 4mg/L. Data from future patients with major burns who receive meropenem should be recorded completely and accurately for future analysis to confirm the effectiveness of the recommendations made.
These recommendations have been made to the multidisciplinary burns team at the Queen Victoria Hospital and the proposals have been agreed for all future treatment of patients with major burns. Adoption of these recommendations may reduce morbidity and mortality in severely burned patients with life-threatening infections.
Chapter 5. Linezolid

5.1. Introduction

Linezolid is the first of a class of antibacterials called the oxazolidinones. This group of antibiotics is active against Gram-positive bacteria, and is generally reserved for treatment of resistant organisms such as meticillin-resistant *Staphylococcus aureus* (MRSA) and glycopeptide-resistant *Enterococcus* (GRE). It is licensed for the treatment of nosocomial and community acquired pneumonia, and also complicated skin and soft tissue infections (Pharmacia&Upjohn 2001b).

Linezolid is (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide (Figure 5.1). It contains a morpholine ring, which is of relevance to its metabolism (see Section 5.1.4.1).
Figure 5.1 Chemical structure of Linezolid. Adapted from Drugbank (2009)
Linezolid contains a morpholine ring (see Section 5.1.4.1).

5.1.1. Mode of action and resistance of linezolid

Linezolid selectively inhibits bacterial protein synthesis. Specifically it binds to a site on the bacterial ribosome (23S of the 50S subunit) near to the interface with the 30S subunit and prevents the formation of a functional 70S initiation complex which is an essential component of the translation process (Lin 1997, Swaney 1998). Resistance may occur by bacteria changing the ribosomal target site of linezolid (Diekema and Jones 2001).

5.1.2. Dose and administration of linezolid

The licensed adult dose is 600mg intravenously or orally twice a day. Linezolid is not licensed for children. The intravenous infusion should be given over 30 –
120 minutes. Dose adjustments are not required in patients with hepatic or renal insufficiency (Pharmacia&Upjohn 2001b).

5.1.3. Linezolid toxicity

Linezolid appears to be generally well-tolerated, with the most common adverse effects at the standard dose being diarrhoea, nausea, vomiting, headache, taste disturbances and candidiasis. It may cause blood dyscrasias, for example anaemia and thrombocytopenia. In rats, doses of 3000mg/kg/day caused decreased activity and ataxia, whilst in dogs, doses of 2000mg/kg/day resulted in vomiting and tremors (Pharmacia&Upjohn 2001b). These doses are far in excess of those received by humans (approximately 20mg/kg/day). The National Poisons Information Service Database states that doses of less than 150 mg/kg are unlikely to cause toxicity in adults (NPIS 2001).

As linezolid is a monoamine oxidase inhibitor, in overdose there is a potential risk of features such as hypertension, tachycardia and agitation, particularly if other MAOIs or drugs such as some antidepressants or pethidine have also been taken (NPIS 2001).

5.1.4. Pharmacokinetics of linezolid

5.1.4.1. Pharmacokinetics of linezolid in healthy volunteers

Linezolid is completely and rapidly absorbed after oral administration, with peak plasma concentrations being reached one to two hours after administration (Stalker, Wajssczuk and Batts 1997; Welshman, Stalker and Wajszczuk 1998). In healthy volunteers, steady-state maximum serum concentrations were approximately 12 and 18mg/L after twice-daily administration of 375 and 625mg oral doses. Trough concentrations were at least 4mg/L for both doses. In another study, using the recommended dosage of 600mg orally twice a day, mean peak and trough plasma concentrations were 21.3mg/L and 6.15mg/L respectively (Pharmacia&Upjohn 2001b). Although concomitant administration of food reduced the maximum plasma concentration by an average of 23%, the area under the plasma concentration-time curve was not affected.
When intravenous doses of 500mg or 625mg were given to 17 volunteers for 7.5 days, steady-state trough levels were 3.51 and 3.84mg/L respectively (Stalker, Wajszczuk and Batt 1997). For both doses, plasma concentrations were greater than 4mg/L for at least 75% of the time. The mean maximum and minimum plasma concentrations following an intravenous dose of 500mg twice a day have been determined to be 15.1mg/L and 3.68mg/L respectively (Pharmacia&Upjohn 2001b).

Linezolid is moderately bound to plasma proteins (31%) and has a steady-state volume of distribution of 40 – 50L (Pawsey, Daley-Yates and Wajszczuk 1996).

Linezolid appears to be primarily metabolised by oxidation of the morpholine ring to form two inactive carboxylic acid metabolites, PNU-142586 and PNU-142300 (Slatter et al. 2001). PNU-142586, the major metabolite, is formed by a chemical oxidation that is non-enzymatic, whereas PNU-142300 is metabolised via the enzymatic beta-lactam pathway. Approximately 35% of linezolid is excreted unchanged in the urine and 60% is accounted for by the two major metabolites (approximately 50% is excreted in the urine, mostly as PNU-142586, and 10% is excreted in the faeces) (Slatter et al. 2001). Additionally there are some minor metabolites. The elimination half-life has been estimated to be approximately 5 hours (Stalker, Wajssczuk and Batt 1997).

Table 5.1 summarises the pharmacokinetics of linezolid following oral and intravenous administration in healthy volunteers (Pharmacia&Upjohn 2000). Of note is the inter-subject variation, with standard deviations being noticeably larger than pharmacokinetic studies of other antibiotics in healthy volunteers. The parameters for the oral suspension are very similar to the oral tablet, except that mean time to reach the peak plasma concentration ($t_{\text{max}}$) for the oral suspension was shorter (0.97±0.88 hours compared with 1.28±0.66 hours).
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Linezolid 600mg tablet</th>
<th>Linezolid 600mg infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Single dose q12h</td>
<td>Single dose q12h</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (mg/L)</td>
<td>12.7 ± 3.96</td>
<td>12.9 ± 1.60</td>
</tr>
<tr>
<td>$C_{\text{min}}$ (mg/L)</td>
<td>6.15 ± 2.94</td>
<td>3.68 ± 2.36</td>
</tr>
<tr>
<td>$t_{\text{max}}$ (h)</td>
<td>1.28 ± 0.66</td>
<td>0.50 ± 0.10</td>
</tr>
<tr>
<td>AUC (mg h/L)</td>
<td>91.4 ± 39.3</td>
<td>80.2 ± 33.3</td>
</tr>
<tr>
<td>$t_{\frac{1}{2}}$ (h)</td>
<td>4.26 ± 1.65</td>
<td>4.40 ± 2.4</td>
</tr>
<tr>
<td>CL (ml/min)</td>
<td>127 ± 48</td>
<td>138 ± 39</td>
</tr>
</tbody>
</table>

Table 5.1 Pharmacokinetic parameters of linezolid in healthy volunteers (Pharmacia&Upjohn 2000)

AUC = area under the plasma concentration – time curve; For single dose this is $\text{AUC}_{0-\infty}$ (area under the curve from zero to infinity), for multiple dose, this is $\text{AUC}_{0-t}$.

CL = systemic clearance; $C_{\text{max}}$ = maximum plasma concentration; $C_{\text{min}}$ = minimum plasma concentration; q12h = every 12 hours; $t_{\frac{1}{2}}$ = elimination half-life; $t_{\text{max}}$ = time from administration to reach $C_{\text{max}}$

5.1.4.2. Pharmacokinetics of linezolid in other populations

Kearns et al (2000) conducted a single-dose pharmacokinetic study of linezolid in 58 infants and children aged 0.3 to 16 years and compared these values with data previously reported from a pharmacokinetic study of linezolid in adults by Stalker, Wajszczuk and Batts (1997). Forty-four subjects received a dose of 1.5mg/kg and fourteen subjects received a dose of 10mg/kg. The authors state that average (mean) values for the apparent volume of distribution observed were slightly larger in children compared with adults. Mean peak plasma levels (normalised to mg/kg dose administered) were slightly lower than in adults and the total plasma clearance also varied between adults compared with children. Children who were less than 40 months old had the highest clearance levels. The authors do not state whether any of these differences are significant. Plasma drug concentrations at 12 and 24 hours after the 10mg/kg dose were below the MIC required to inhibit 90% of susceptible bacteria in vitro. Kearns et al (2000) suggested that their data support a dose of 10mg/kg every eight or twelve hours to be used in future studies of drug efficacy and safety.
<table>
<thead>
<tr>
<th></th>
<th>1.5mg/kg dose</th>
<th>10mg/kg dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vd (l/kg)</td>
<td>0.75 ± 0.18</td>
<td>0.66 ± 0.18</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (mg/L)</td>
<td>2.5 ± 0.8</td>
<td>15.3 ± 4.7</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; dose normalised (mg/L/mg dose)</td>
<td>0.11 ± 0.06</td>
<td>0.07 ± 0.06</td>
</tr>
<tr>
<td>t½ (h)</td>
<td>3.1 ± 1.1</td>
<td>2.7 ± 0.9</td>
</tr>
<tr>
<td>Cl (L/kg/hr)</td>
<td>0.36 ± 0.16</td>
<td>0.26 ± 0.11</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-∞&lt;/sub&gt; (mg*h/L)</td>
<td>5.22 ± 3.18</td>
<td>44.2 ± 17.0</td>
</tr>
</tbody>
</table>

Table 5.2 Single dose pharmacokinetics of linezolid in children and infants adapted from Kearns et al (2000)

Vd = volume of distribution; C<sub>max</sub> = maximum plasma concentration; t½ = elimination half-life; CL = systemic clearance; AUC<sub>0-∞</sub> = the area under the plasma concentration vs time curve from 0 to infinity.

5.1.4.3. Pharmacokinetics of linezolid in patients with burns

A literature search up to 2002 was unable to reveal any pharmacokinetic studies in burns patients. There has been a report (Atkins et al. 2002) of two patients with large burns (45% and 43% total burns surface area) being successfully treated with linezolid. Both patients had vancomycin-resistant enterococcal septicaemia and were treated with 600mg intravenously twice a day.

5.1.5. Pharmacodynamics of linezolid

Linezolid exhibits time-dependent killing. The percentage of the dose interval above the minimum inhibitory concentration (T>MIC) and the ratio of the area under the serum concentration vs time curve to the minimum inhibitory concentration (AUC/MIC ratio) are thought to be the best determinants of its efficacy.
Using a maximum effect model in mice (Andes, Van Ogtrop and Craig 2000), time above the MIC was the major predictor of linezolid’s efficacy against penicillin-susceptible *Streptococcus pneumoniae*, ($R^2 = 84\%$ for $T>MIC$, vs $42\%$ for $\text{AUC}_{0-24}/\text{MIC}$ and $39\%$ for $\text{C}_{\text{max}}/\text{MIC}$). No indicator correlated with efficacy against *Staphylococcus aureus* which was thought to be due to lower rates of *in vivo* killing. The percent of time above the MIC required for a bacteriostatic effect varied from 33 to 49% for pneumococci (mean 40%) and 33 to 59% for staphylococci (mean 41%). Linezolid had an *in vivo* post-antibiotic effect of 3-4 hours for *S. pneumoniae* and *S. aureus*. The authors concluded that based upon a pharmacokinetic goal of 40% of the time above the MIC, a dosage of 500mg given either intravenously or orally would achieve success against organisms with MICs as high as 4mg/L.

Further studies in mice by Andes *et al* (2002) revealed the major predictor of efficacy against penicillin-susceptible *S. pneumoniae* to be the $\text{AUC}_{0-24}$ to MIC ratio ($R^2 = 82\%$ versus 57% for $T>MIC$ and 59% for $\text{C}_{\text{max}}/\text{MIC}$). The marker was less clear for *S. aureus* with an $R^2$ of 75% for both $\text{AUC}_{0-24}/\text{MIC}$ ratio and $T>MIC$, and a value of 65% for $\text{C}_{\text{max}}/\text{MIC}$. The authors concluded that based on a pharmacokinetic goal of a 24-hour $\text{AUC}_{0-24}/\text{MIC}$ of 50 to 100, a dosage regimen of 600mg twice daily, given orally or intravenously, would achieve success against organisms with MICs as high as 4mg/L.

Gentry-Nielsen *et al* (2002) studied the pharmacodynamics of linezolid in an immunocompetent rat model of pneumococcal pneumonia. Using doses of 50mg/kg/day seven out of twelve rats died from their infection. In the group of twelve rats receiving twice this dose, only one rat died. The mean $T>MIC$ of the two groups were 31.1% and 39% respectively. The authors concluded that parameters predictive of outcome were a $T>MIC$ of at least 39%, and an $\text{AUC}_{0-12}/\text{MIC}$ ratio greater than 147.
5.2. Aims and objectives

As outlined in Chapter 1, Section 1.11 the aim of this study was to investigate the pharmacokinetic parameters of antibiotics when administered to patients with major burns and to produce dosing guidelines for the use of these antibiotics.

Objectives were:

- To measure the serum concentrations of linezolid in adults with major burns (>15% total body surface area) receiving this antibiotic for treatment of severe infections.
- To compare the serum concentrations with those required to treat likely infections.
- To calculate pharmacokinetic parameters such as volume of distribution, clearance and elimination half-life.
- To compare pharmacokinetic parameters calculated in this study of severely burned patients with other populations.
- To investigate the influence of patient factors on the serum concentrations and pharmacokinetic parameters.
- To produce dosage guidelines for the use of linezolid in adults with major burns.

5.3. Method

The methodology for the pharmacokinetic study of linezolid, together with the other antibiotics is outlined in Chapter 3. Linezolid was administered as a 30-minute intermittent infusion in line with guidelines developed by the Researcher in the role of clinical pharmacist.

For this pharmacokinetic study in burns patients, the marker of efficacy was selected for serum concentrations as above the MIC for at least 40% of the dose interval. This was selected over the AUC/MIC ratio due to the ease of adjusting doses in clinical practice. An MIC of 4mg/L was selected as this was...
the susceptibility breakpoint for linezolid against Gram-positive organisms (BSAC 2002).

HPLC analysis was performed as described by Tobin et al (2001), and was discussed in Chapter 3, Section 3.7. Pharmacokinetic parameters were calculated using WinNonlin® using a non-compartmental model.

5.4. Results

5.4.1. Demographics

Although the target recruitment number was twelve patients, only four patients required linezolid during the study period. Patients ranged in age from 27 to 64 years, with the percentage burn varying from 17 to 53%. Two patients were male and three had inhalational injury. All sustained flame burns. The time in intensive care varied from 8 to 126 days (Table 5.3)

None of the patients had a combined age plus % TBSA burn of over 100, although only two survived their injury. Of those who died, one was acutely unwell when the linezolid was commenced and died only eight days after his burn. The two patients with the highest ABSI scores both survived, whereas the other two patients died.
<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Gender</th>
<th>Age</th>
<th>Cause of burn</th>
<th>Type of burn</th>
<th>% TBSA burn</th>
<th>Inhalation injury</th>
<th>ABSI Score*</th>
<th>Outcome</th>
<th>Length of stay in ITU (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>27</td>
<td>Caravan explosion</td>
<td>Flame</td>
<td>52</td>
<td>Y</td>
<td>10</td>
<td>Survived</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>64</td>
<td>House Fire</td>
<td>Flame</td>
<td>17</td>
<td>Y</td>
<td>8</td>
<td>Died</td>
<td>8 days</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>40</td>
<td>Assault - petrol</td>
<td>Flame</td>
<td>53</td>
<td>Y</td>
<td>11</td>
<td>Survived</td>
<td>40 days</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>59</td>
<td>Candle ignited clothes</td>
<td>Flame</td>
<td>32</td>
<td>N</td>
<td>9</td>
<td>Died</td>
<td>126</td>
</tr>
</tbody>
</table>

* ABSI Score

<table>
<thead>
<tr>
<th>Threat to life</th>
<th>Probability of Survival</th>
<th>Score</th>
<th>Threat to life</th>
<th>Probability of Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 – 3</td>
<td>Very Low</td>
<td>0.99</td>
<td>8 – 9</td>
<td>Serious</td>
</tr>
<tr>
<td>4 – 5</td>
<td>Moderate</td>
<td>0.98</td>
<td>10 – 11</td>
<td>Severe</td>
</tr>
<tr>
<td>6 – 7</td>
<td>Moderately severe</td>
<td>0.8 – 0.9</td>
<td>12 – 13</td>
<td>Maximum</td>
</tr>
</tbody>
</table>

* Table 5.3. Patient demographics

The table describes the demographics of the patients recruited to the linezolid arm of the study.
Linezolid was used to treat MRSA infections, although other Gram-positive organisms identified at the time were *coagulase-negative staphylococci*, *streptococci* spp and *Bacillus cereus*. Other antimicrobial therapy was used, where appropriate to treat Gram-negative organisms, such as *Pseudomonas Aeruginosa*, *Enterococcus* spp, *Klebsiella oxytoca* and *Enterobacter cloacae*.

### 5.4.2. Pharmacokinetics

Six sets of blood samples were collected. Patient 1 had two sets of samples taken as the frequency of dosing was increased to every eight hours. Patient 4 received two courses of linezolid and a set of samples was taken each time. As with other studies of antibiotics in burns patients there was wide inter-patient variation in some of the pharmacokinetic parameters calculated (Table 5.4)

<table>
<thead>
<tr>
<th>Pt no</th>
<th>Dosing interval (t)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (mg/L)</th>
<th>AUC&lt;sub&gt;0-1&lt;/sub&gt; (mg/L.h)</th>
<th>AUC&lt;sub&gt;0-24&lt;/sub&gt; (mg/L.h)</th>
<th>t&lt;sub&gt;1/2&lt;/sub&gt; (h)</th>
<th>V (L)</th>
<th>V (L/kg)</th>
<th>CL (L/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12-hourly</td>
<td>16.4</td>
<td>25.7</td>
<td>51.4</td>
<td>1.4</td>
<td>40.9</td>
<td>0.55</td>
<td>20.8</td>
</tr>
<tr>
<td>3</td>
<td>12-hourly</td>
<td>15.8</td>
<td>54.0</td>
<td>108.0</td>
<td>2.7</td>
<td>38.0</td>
<td>0.58</td>
<td>9.8</td>
</tr>
<tr>
<td>4</td>
<td>12-hourly</td>
<td>19.3</td>
<td>75.9</td>
<td>151.8</td>
<td>5.3</td>
<td>50.0</td>
<td>0.50</td>
<td>6.5</td>
</tr>
<tr>
<td>4</td>
<td>12-hourly</td>
<td>15.6</td>
<td>57.4</td>
<td>114.8</td>
<td>4.4</td>
<td>54.2</td>
<td>0.77</td>
<td>8.5</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>16.8</td>
<td>53.3</td>
<td>106.5</td>
<td>3.5</td>
<td>45.8</td>
<td>0.6</td>
<td>11.4</td>
</tr>
<tr>
<td>S.D.</td>
<td></td>
<td>1.7</td>
<td>20.7</td>
<td>41.5</td>
<td>1.7</td>
<td>7.6</td>
<td>0.11</td>
<td>6.4</td>
</tr>
<tr>
<td>1</td>
<td>8-hourly</td>
<td>19.5</td>
<td>45.8</td>
<td>137.4</td>
<td>1.9</td>
<td>34.9</td>
<td>0.47</td>
<td>12.9</td>
</tr>
<tr>
<td>2</td>
<td>8-hourly</td>
<td>24.5</td>
<td>119.8</td>
<td>359.4</td>
<td>9.8</td>
<td>55.2</td>
<td>0.52</td>
<td>3.9</td>
</tr>
<tr>
<td>Mean</td>
<td>(for all six values)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S.D.</td>
<td></td>
<td>3.1</td>
<td>8.7</td>
<td>0.11</td>
<td></td>
<td></td>
<td></td>
<td>5.9</td>
</tr>
</tbody>
</table>

**Table 5.4** Pharmacokinetic parameters for linezolid 600mg IV over 30 minutes.

Six sets of blood samples were collected for four patients. Patient 2 had two sets of samples taken as he required a dose increase. Patient 4 received 2 courses of linezolid and a set of blood samples were taken for each course.
Linezolid pharmacokinetics appeared to fit a two-compartment model, with the distribution phase lasting up to 2 hours. The mean half-life, volume of distribution and clearances calculated in this study are listed together with values from other studies (Table 5.5).

<table>
<thead>
<tr>
<th>N =</th>
<th>t 1/2 (h)</th>
<th>Cl (L/hr)</th>
<th>Vd (L)</th>
<th>AUC_{0-12} (mg/L.h)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with burns</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4.4 ± 3.1</td>
<td>10.4 ± 5.9</td>
<td>45.5 ± 8.7</td>
<td>70.3* ± 47.7</td>
<td>This study</td>
</tr>
<tr>
<td>8**</td>
<td>2.1 ± 1.0</td>
<td>20.9 ± 12.4</td>
<td>50.8 ± 16.8</td>
<td>42.5*** ± 24.0</td>
<td>Lovering et al (2009)</td>
</tr>
<tr>
<td>Healthy subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24****</td>
<td>4.8 ± 1.7</td>
<td>7.4 ± 2.4</td>
<td>45.5 ± 4.87</td>
<td>93.4 ± 32.3</td>
<td>Stalker et al (2003)</td>
</tr>
</tbody>
</table>

Table 5.5 Comparison of the pharmacokinetic parameters of linezolid from this study compared with published values

Neither of the published studies include data from patients with renal impairment, data is calculated from dose of 600mg IV twice daily at steady-state, unless otherwise indicated. * Includes estimates for the 8 hourly doses **First dose kinetics *** AUC_{0-∞} **** 625mg dose. Cl = total clearance, Vd = volume of distribution, AUC_{0-12} = the area under the concentration vs time plot from 0 to 12 hours.

5.4.3. Relationship between dose and effect

Patients were usually commenced on a dose of 600mg every twelve hours. The exception to this was Patient 2, who received an initial dose of 600mg every eight hours. This was because Patient 1 had required a dose increase, and due to the critically ill status of Patient 2, the potential benefits of receiving a therapeutic dose earlier in therapy were thought by the clinician to outweigh the risk of administering a higher dose than necessary. Figures 5.2a and 5.2b show the concentrations for each patient for eight-hourly and twelve-hourly regimens respectively.
Figure 5.2a. Linezolid concentrations for doses of 600mg twelve-hourly

The figures show the serum concentrations of linezolid for each patient following the administration of a dose of 600mg intravenously, infused over half an hour. It can be seen in the figures that dosing was therapeutic (i.e. serum concentrations were above 4m/L for at least 40% of the dose interval) for three
of the four patients who received a dose of 600mg every twelve hours, and for both of the patients who received a dose of 600mg every eight hours.

Patient 1 was the only patient who required an increase in dose frequency. Patient 4 received two courses of linezolid, and both times, serum concentrations were above 4mg/L for more than 40% of the dose interval. The predicted AUC/MIC ratio and T>MIC were calculated for MICs of 1mg/L, 2mg/L and 4mg/L (Table 5.6). It can be seen from this that at the dose of 600mg twelve-hourly Patient 1 would have only achieved a T>MIC of at least 40% if the MICs were 1mg/L or less.

<table>
<thead>
<tr>
<th>Pt No</th>
<th>Dose frequency</th>
<th>MIC 1mg/L</th>
<th>AUC(_{0-24}/\text{MIC}) (h)</th>
<th>% T&gt;MIC</th>
<th>MIC 2mg/L</th>
<th>AUC(_{0-24}/\text{MIC}) (h)</th>
<th>% T&gt;MIC</th>
<th>MIC 4mg/L</th>
<th>AUC(_{0-24}/\text{MIC}) (h)</th>
<th>% T&gt;MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12-hourly</td>
<td>51</td>
<td>45</td>
<td>26</td>
<td>33</td>
<td>13</td>
<td>22</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>8-hourly</td>
<td>137</td>
<td>98</td>
<td>69</td>
<td>70</td>
<td>34</td>
<td>45</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>8-hourly</td>
<td>359</td>
<td>100</td>
<td>180</td>
<td>100</td>
<td>90</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>12-hourly</td>
<td>108</td>
<td>90</td>
<td>54</td>
<td>67</td>
<td>27</td>
<td>46</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>12-hourly</td>
<td>152</td>
<td>100</td>
<td>76</td>
<td>100</td>
<td>38</td>
<td>89</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>12-hourly</td>
<td>115</td>
<td>100</td>
<td>57</td>
<td>98</td>
<td>29</td>
<td>58</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Table 5.6 Estimated AUC/MIC ratio and T>MIC with differing MICs*

Bold type indicates a T>MIC of at least 40% i.e. therapeutic serum concentrations.

Changing the method of administration to continuous infusion would have achieved a T>MIC of 100% for Patient 1 at the dose of 1,200mg/24 hours if the MIC was 2mg/L or less. However to achieve steady-state serum concentrations above 4mg/L would have required doses higher than 1,800mg/day (Table 5.7).
### Table 5.7 Predicted serum steady state serum concentrations (mg/L) for study patients if had received linezolid by continuous infusion

<table>
<thead>
<tr>
<th>Patient no</th>
<th>Total daily dose 1,200mg</th>
<th>Total daily dose 1,800mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.4</td>
<td>3.6</td>
</tr>
<tr>
<td>2</td>
<td><strong>12.8</strong></td>
<td><strong>19.2</strong></td>
</tr>
<tr>
<td>3</td>
<td>5.1</td>
<td>7.7</td>
</tr>
<tr>
<td>4</td>
<td>7.7</td>
<td>11.5</td>
</tr>
</tbody>
</table>

Bold type indicates a predicted serum concentration above 4mg/L i.e. therapeutic serum concentrations.

### 5.4.4. Correlation with patient factors

The patient who required a dose increase (Patient 1) was noticeably younger than those who did not, and possessed a higher creatinine clearance value. Otherwise there were no remarkable differences in the patient factors.

Linezolid had a shorter half-life, smaller AUC and greater clearance in Patient 1, compared with the other patients. All patients had similar volumes of distribution (Table 5.8).
<table>
<thead>
<tr>
<th>Patient number</th>
<th>Age (years)</th>
<th>Initial % TBSA burn</th>
<th>Initial % FT BSA</th>
<th>Serum creatinine (μmol/L)</th>
<th>Measured creatinine clearance (ml/min)</th>
<th>Albumin (g/L)</th>
<th>Day post-burn of sampling</th>
<th>t1/2 (h)</th>
<th>V (L)</th>
<th>V (L/kg)</th>
<th>CL (L/h)</th>
<th>AUC_{0-12}</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>64</td>
<td>17</td>
<td>17</td>
<td>49</td>
<td>&lt;10</td>
<td>129</td>
<td>8</td>
<td>9.8</td>
<td>55</td>
<td>0.52</td>
<td>3.9</td>
<td>160*</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td>53</td>
<td>53</td>
<td>40</td>
<td>130</td>
<td>17</td>
<td>20</td>
<td>2.7</td>
<td>38</td>
<td>0.58</td>
<td>9.8</td>
<td>54</td>
</tr>
<tr>
<td>4**</td>
<td>59</td>
<td>32</td>
<td>22</td>
<td>51</td>
<td>129</td>
<td>16</td>
<td>10</td>
<td>5.3</td>
<td>50</td>
<td>0.50</td>
<td>6.5</td>
<td>76</td>
</tr>
</tbody>
</table>

**Group A. Patients where 1g 12-hourly dose was predicted to be therapeutic**

**Group B. Patient predicted to require more frequent dosing**

| 1              | 27          | 52                  | 25               | 38                        | 202                                   | 17           | 14                       | 1.4***   | 41***  | 0.55***  | 21***    | 26***     |

*Table 5.8 Patient factors and pharmacokinetic parameters according to the dose required*

* Predicted ** First of samples *** Calculated from samples taken when on 12-hourly dosage regimen
5.5. Discussion

This is the first study of steady-state linezolid pharmacokinetics in patients with severe burns. One out of the four patients did not achieve the target MIC of 4mg/L for at least 40% of the dose interval at the standard dose of 600mg every twelve hours, indicating that some patients with severe burns may require higher than recommended doses. This indicates that patients may benefit from tailored dosing instead of using the standard dose of 600mg every twelve hours.

It was disappointing that data was collected on only four patients, although from a clinical view, it was good that so few were infected by multi-resistant Gram-positive organisms. At the commencement of the thesis, other burns centres indicated that they wished to join the study, and therefore it was predicted that the recruitment target of twelve patients would be reached. As only four patients were actually recruited, statistical analysis could not be undertaken.

There was a wide interpatient variation in clearance, a parameter principally related to elimination. For the peak serum concentrations and volumes of distribution – parameters related primarily to distribution – there was much less variation. Linezolid had a noticeably smaller half-life and a greater clearance in Patient 1 who required the dose increase, but there was less difference in the other parameters, particularly the volume of distribution. Patient 1 had a much higher creatinine clearance (202ml/min), which suggests that altered pharmacokinetics may be due to the hypermetabolic response. Such response may increase elimination, through enhanced metabolism or renal excretion and/or loss through the burn wound.

Linezolid in Patient 2 had the largest peak concentration, $\text{AUC}_{0-t}$ (despite $t$ being only 8 hours) and half-life, and the lowest clearance compared with any of the other patients. There were no noticeable differences in his characteristics compared with the other patients who did not require a dose increase. This patient was critically ill at the time of sampling and died later that day. It is possible that there was a significant change in his renal and/or hepatic function during the sampling period, which may explain the differences.
5.5.1. **Comparison of linezolid pharmacokinetics with other studies**

Comparing linezolid mean pharmacokinetic parameters in patients in this study with those measured in healthy volunteers (Stalker *et al.* 2003), it was surprising how similar the mean volume of distributions were; 45.5 ± 8.7L vs 45.5 ± 4.87L respectively (Table 5.5). It might be expected that this value would be higher in patients with burns because of increased extravascular fluid, particularly as linezolid has been shown to have good tissue penetration in healthy adults (Gee *et al.* 2001). However Buerger *et al.* (2006) found that distribution into the interstitial space fluid in both sub-cutaneous tissue and muscle varied greatly between critically ill patients with sepsis or septic shock. They found that 8.3% of patients showed a very low distribution into the ISF, which they suggested may, at least have been in part, have been due to impaired perfusion of the microcirculation that has been observed in septic patients. It may therefore be that in patients with burns the potential increase in volume of distribution due additional extravascular fluid is counteracted by a reduction in the tissue penetration of linezolid. Further studies are required to confirm this.

In 2009, Lovering *et al.* recorded a significantly shorter mean half-life (P=0.016), and smaller mean AUC_{0-∞} (P = 0.016) following a single dose of linezolid in eight patients with major burns (>20% TBSA) compared with eight healthy volunteers. However the volumes of distribution were similar (P=0.383), and although mean total clearance was much greater in the thermally injured patients, the large interpatient variation meant that the difference was not significant (P = 0.063). The mean volume of distribution was similar to those seen in the current burns study, but there were differences in the other parameters. The creatinine clearances of patients in the study by Lovering *et al.* (2009) were not published, but the patients had a mean age of 37 years, which was younger than in this study (mean age 47). Mean weights of patients in the study by Lovering *et al.* (2009) were lower than this study (64kg vs 86kg), but the mean TBSA was similar (41% vs 39%). Patient numbers 1 and 3 in the current study had ages and weights within the ranges of the study by Lovering *et al.* (2009). They also had pharmacokinetic parameters which were much closer to those of the study by Lovering *et al.* (2009) when compared with the values obtained for the other two patients. This suggests that findings from this
burns study may be consistent with that of Lovering et al (2009). It may therefore be that younger adults may be more hypermetabolic which results in altered pharmacokinetics compared with older patients, and so an increase in the required dose. It should be noted that Lovering et al (2009) calculated first dose kinetic parameters, whereas in this study kinetics were calculated at steady-state. Referring back to Table 5.1 however, it can be seen that parameters in healthy subjects were similar after single and multiple intravenous dosing. Lovering et al (2009) concluded that pharmacokinetics of linezolid are altered in patients with major burns mainly due to an increase in non-renal clearance, and as a result the dose may need to be administered more frequently.

The majority of the research of what patient factors affect the hypermetabolic response in thermally injured patients has been performed in children. Jeschke et al (2007) predicted the resting energy expenditure of one hundred and eighty-nine patients according to their burn size (<40%, 40–59%, 60–79% and >80%, matched for age and gender) and found that it was highest in the >80% group, followed by the 60–70% group. Jesche et al (2008) also predicted the resting energy expenditure according to age in 188 paediatric patients. They found that this was highest in the 10 to 18 year olds, lowest and in the 0 to 3.9 years old, with the value for children from 4 to 9.9 being in-between. There is also some evidence in children to suggest that males may also have greater hypermetabolic response to burn injury than females (Mlcak et al. 2006).

In this study, the greatest hypermetabolic response, as indicated by creatinine clearance, was seen in the youngest patient. As the patients were all adult, it is possible that the hypermetabolic response peaks in young adulthood, and these are the patients who may require an increased dose of linezolid. This may be confirmed by data collection on future patients.

Age does not appear to be a significant factor in the pharmacokinetics of linezolid in healthy volunteers. In a comparison of patients aged 18 to 40 years with those aged over 65 years (Sisson, Jungbluth and Hopkins 2002), the younger age group had a significantly higher mean creatinine clearance.
(although both were considered to have normal renal function), and higher mean renal linezolid clearance. As a much higher proportion was cleared non-renally than renally (where there were no differences between the age groups) dosage adjustments were thought unlikely to be necessary. The same study also investigated the effect of gender on pharmacokinetics, and found that females appear to have a lower total clearance and volume of distribution, although this was not thought to be clinically relevant.

The study by Lovering et al (2009) indicated that it is the increase in non-renal clearance that affects the pharmacokinetics of linezolid in patients with burns. Mean renal clearances were very similar between burned and non-burned patients (P=0.156). Mean non-renal clearance was 80.4ml/min in healthy volunteers, whereas this figure was 323ml/min in the burned patients, although the difference was not significant (P=0.063). Therefore factors such as loss of drug through the burn wound, or increased oxidation of the morpholine ring may be responsible for the greater clearance of linezolid. The latter may be due to oxidative stress that occurs in critically ill patients (Meagher et al. 2003).

5.5.2. Pharmacodynamic and pharmacokinetic studies of linezolid from 2002 to 2010 – a review of the literature

In 2002 when this study was commenced, the oxazolidinones were a new class of drugs and few pharmacodynamic studies had been undertaken. Therefore it is necessary to review the literature from this time, to determine whether 40% of the dose interval above 4mg/L is still the best marker of efficacy (Table 5.9).

In 2003, Meagher et al found that the AUC\textsubscript{0-24} ranged from 57 to 581 mg/L.h in 318 adults treated with linezolid in a compassionate use programme of infections caused by multi-resistant Gram-positive organisms. These patients received a dose of 600mg either intravenously or orally every twelve hours. Despite the variation in the AUC there were high rates of clinical cure and microbiological success. Data from 288 seriously ill patients, who appear to be from the same group, have been used for pharmacodynamic evaluation (Rayner et al. 2003). Pathogens isolated from different sites were mainly
MRSA and vancomycin-resistant *Enterococcus faecium.* The clinical cure in these patients receiving a dose of 600mg IV twelve-hourly was 92.1%, and microbiological eradication was 83.7%. The probability of both clinical cure and microbiological eradication mostly depended on the site of infection and the MIC of the infecting organisms. It was probable that both markers of efficacy were related to the $AUC_{0-24}/MIC$ ratio and the $T>MIC$. The authors concluded that a dose of 600mg every twelve hours should be effective against pathogens up to 4mg/L.

Humphrey *et al* (2003) undertook studies in a gerbil model of *S. pneumoniae*-induced acute otitis media. By measuring plasma and ear fluid concentrations of linezolid, they found that bacterial eradication was associated with a $T>MIC$ of at least 42%, a $C_{max}/MIC$ ratio of at least 3.1 and an $AUC_{0-24}/MIC$ ratio of at least 30h.

In their study of a rabbit model of endocarditis infected by *S. aureus*, Tsagonos *et al* (2008) concluded that orally administered linezolid is effective in limiting bacterial growth. From day 2, serum concentrations were above the MIC for the whole of the dosing interval. This confirmed that effective treatment occurred when $T>MIC$ was 100%, but the study was not designed to show whether a $T>MIC$ of less than 100% would also have been effective.

An *in vitro* dynamic model was used to assess the effect of different $AUC_{0-24}/MIC$ ratios on bacterial growth of *S. aureus* (Strukova *et al.* 2009). As the $AUC_{0-24}/MIC$ increased, the minimal number of survivors decreased, and the cumulative effect of five days of twice-daily treatment increased. By comparing the pharmacodynamics of linezolid with those of ciprofloxacin, which has an established $AUC_{0-24}/MIC$ target, Strukova *et al* (2009) concluded that their findings were consistent with the target $AUC_{0-24}/MIC$ of 80 to 120 proposed by Rayner *et al* (2003). This study did not consider the effect of $T>MIC$.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study type</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andes et al (2000)</td>
<td>Mouse model</td>
<td>T&gt;MIC major predictor against \textit{S. pneumoniae}. No clear indicator for \textit{S. aureus}. Target of T&gt;MIC of 40% would achieve success against MICs of organisms with MICs up to 4mg/L for a dose of 500mg 12-hourly.</td>
</tr>
<tr>
<td>Andes et al (2002)</td>
<td>Mouse model</td>
<td>AUC/MIC ratio major predictor of efficacy against \textit{S. pneumoniae}. Less clear for \textit{S. aureus}. Pharmacokinetic goal of AUC\textsubscript{0-24}/MIC of 50 to 100 proposed.</td>
</tr>
<tr>
<td>Gentry-Nielsen et al (2002)</td>
<td>Rat model</td>
<td>Parameters predictive of outcome were a T&gt;MIC of at least 39%, and an AUC\textsubscript{0/24}/MIC ratio greater than 147.</td>
</tr>
<tr>
<td>Rayner et al (2003)</td>
<td>288 patients with multi-resistant G+ve organisms</td>
<td>Highest chances of microbiological and clinical success appeared to be an AUC\textsubscript{0-24}/MIC ratio of 80 to 120, and / or when T&gt;MIC was 100%.</td>
</tr>
<tr>
<td>Tsaganos et al (2008)</td>
<td>Rabbit model of infective (\textit{S. aureus}) endocarditis</td>
<td>Serum concentrations were above the MIC from second day of treatment for the whole of the dose interval, which was effective.</td>
</tr>
<tr>
<td>Moise et al (2008)</td>
<td>Retrospective analysis comparing patients with MRSA of MIC ≤2mg/L with MIC of 4mg/L</td>
<td>Higher clinical success rate when MIC≤2mg/L. Time to bacterial kill was significantly longer when MIC was 4mg/L. Authors commented that with 2mg/L the AUC/MIC ratio was likely to be greater than 83, but with 4mg/L is was likely to be less than 83.</td>
</tr>
<tr>
<td>Strukova et al (2009)</td>
<td>\textit{In vitro} dynamic model</td>
<td>Results were consistent with an already proposed target AUC\textsubscript{0-24}/MIC of 80 to 120.</td>
</tr>
</tbody>
</table>

\textbf{Table 5.9 Linezolid pharmacodynamic studies}

T>MIC = percentage of the dose interval above the minimum inhibitory concentration, AUC/MIC = area under the serum concentration vs time curve / minimum inhibitory concentration, AUC\textsubscript{0-24}/MIC = area under the serum concentration vs time curve / minimum inhibitory concentration for a 24 hour period, Cmax = maximum (peak) serum concentration.

Since 2002, there have been several studies applying the pharmacokinetics of linezolid in different populations to pharmacodynamic targets (Table 5.10). The majority of studies have used AUC\textsubscript{0-24}/MIC as the marker of efficacy, with this figure generally being at least 80. Where T>MIC has been used, this has been at least 85%. The references most widely quoted are that of the mouse model.
(Andes et al. 2002) and the study in patients (Rayner et al. 2003). As the latter is the only patient study, and a large number of patients were included, considering the critically ill status of severely burned patients, the best option may be to aim for T>MIC for the whole of the dose interval and AUC$_{0-24}$/MIC of at least 80 h.

<table>
<thead>
<tr>
<th>Population</th>
<th>Marker of efficacy</th>
<th>Conclusions</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 healthy volunteers</td>
<td>T&gt;MIC ≥ 40%</td>
<td>C$_{\text{min}}$ at steady-state was close to 4mg/L.</td>
<td>Stalker et al (2003)</td>
</tr>
<tr>
<td>12 adults with cystic fibrosis</td>
<td>AUC$_{0-24}$/MIC 83 to 100</td>
<td>Standard doses may not be sufficient to reach this target even for MICs of 1mg/L</td>
<td>Bosso et al (2004)</td>
</tr>
<tr>
<td>20 patients undergoing continuous venovenous haemofiltration</td>
<td>T &gt; MIC</td>
<td>In infections caused by pathogens with MICs of 4mg/L, T&gt;MIC was 57 ± 32%. Higher doses may be required in certain cases.</td>
<td>Meyer et al (2005)</td>
</tr>
<tr>
<td>16 critically ill patients with ventilator-associated pneumonia</td>
<td>AUC$_{0-24}$/MIC 50 to 100</td>
<td>Dose of 600mg IV 12-hourly is sufficient against MICs as high as 4mg/L in both serum and epithelial lining fluid.</td>
<td>Boselli et al (2005)</td>
</tr>
<tr>
<td>28 critically ill adults</td>
<td>T &gt; MIC ≥ 85% AUC$_{0-24}$/MIC &gt; 100</td>
<td>T &gt; 4mg/L ≥ 90% of dose interval, which thought likely to be effective.</td>
<td>Whitehouse et al (2005)</td>
</tr>
<tr>
<td>Monte Carlo simulation</td>
<td>AUC$_{0-24}$/MIC &gt; 82.9</td>
<td>Target was likely to be achieved for staphylococcal isolates.</td>
<td>Kuti et al (2008)</td>
</tr>
<tr>
<td>10 children with cystic fibrosis being treated for MRSA infection</td>
<td>AUC$<em>{0-24}$/MIC &gt; 80 (1) AUC$</em>{0-24}$/MIC &gt; 80 (2) C$_{\text{max}}$/MIC ≥ 9.1 (3) T &gt; MIC ≥ 40</td>
<td>Targets at standard dose were achieved in 0/14 (1), 8/14 (2) and 9/14 (3). All treatments were clinically effective, but MRSA persisted in cultures.</td>
<td>Santos et al (2009)</td>
</tr>
<tr>
<td>8 adults with major burns</td>
<td>AUC$_{0-24}$/MIC &gt; 80 for S.aureus</td>
<td>A dose of 600mg 12-hourly may not be effective where the MIC is greater than 1mg/L</td>
<td>Lovering et al (2009)</td>
</tr>
<tr>
<td>MRSA mediastinitis in 4 children</td>
<td>AUC$<em>{0-24}$/MIC &gt; 100% (1) AUC$</em>{0-24}$/MIC 80 -120 (2) T&gt;MIC 100%</td>
<td>Dose of 10mg/kg 8-hourly recommended. Monitor trough levels to be kept above MIC.</td>
<td>Kosova et al (2009)</td>
</tr>
</tbody>
</table>

Table 5.10 Pharmacokinetic studies of linezolid using a target marker of efficacy
T>MIC = percentage of the dose interval above the minimum inhibitory concentration, AUC$_{0-24}$/MIC = area under the serum concentration vs time curve / minimum inhibitory concentration for a 24 hour period, C$_{\text{max}}$ = maximum (peak) serum concentrations
5.5.3. Linezolid dosing options for patients with major burns

As concluded in Section 5.5.2, evidence suggests that the target of efficacy for linezolid should be a T>MIC for the whole of the dose interval and AUC\textsubscript{0-24}/MIC of at least 80h. In the study of first dose pharmacokinetics of linezolid in patients with burns (Lovering et al. 2009), a target of AUC\textsubscript{0-24}/MIC > 80 for \textit{S.aureus} was discussed. A mean AUC\textsubscript{0-24} of 85 measured in their patients, led the authors to suggest that treatment at standard doses may not be effective where the MIC is greater than 1mg/L.

MICs of infecting organisms were not measured in this burns study. This was mainly due to the time and cost associated with MIC measurement. Where susceptibilities were recorded, no linezolid resistance was reported, and hence the reason why the breakpoint of 4mg/L was selected as the target MIC. However it is likely that some or all of the MICs were lower than 4mg/L. A study by Wilson et al (2006) measured the MICs of Gram-positive organisms in patients treated in general intensive care units at an NHS trust in London. For MRSA, the MIC\textsubscript{50} was 1.5 and MIC\textsubscript{90} was 2mg/L, but ranged from 0.38 to 4mg/L. Values for MSSA varied slightly by site but were similar to those of MRSA.

Using the targets of an AUC/MIC ratio of at least 80 and a T>MIC of 100% it can be seen in Table 5.6 that for Patient 1, serum concentrations would have been sub-therapeutic at a dose of 600mg every twelve hours even for MICs of 1mg/L. With an eight-hourly regimen bacteria with MICs of 1mg would have probably been effectively treated, but not 2mg/L or higher. By contrast when Patient 2 received a dose of 600mg every eight hours, effective treatment was likely to have been achieved against all bacteria with MICs up to 4mg/L. For the other two patients a dose of 600mg every twelve hours against organisms with an MIC of 1mg/L was likely to be effective, but possibly not against organisms with higher MICs.

Given the possible consequences of under-treating Gram-positive infections in patients with large burns, it could be suggested that a larger total daily dose than 1,200mg should be given to these patients. However, from the data in this
current study, and that of Lovering et al (2009), it is predicted that a much higher total daily dose is likely to be needed to attain of a target of 4mg/L in some patients. There is limited information regarding administration of doses above those stated in the manufacturer’s license. Therefore to avoid excessive dosing, rather than using an MIC of 4mg/L, there is justification for MICs to be measured and the target set accordingly. Unlike meropenem, linezolid is rarely used as empiric therapy. Instead it is commenced following the isolation of multi-resistant Gram-positive organisms and the MICs can be measured. Where the MIC is not known, a target of 4mg/L should remain. In practice it is easier to measure the T>MIC than the AUC. Therapy should be directed to achieve a T>MIC (or 4mg/L) of 100% but be balanced against the risk of toxicity if using higher doses.

Ackerman et al (2007) evaluated the adverse effect profile of twice-daily linezolid by measuring the leukocyte and platelet count in 76 patients with major burns (94 courses) requiring treatment for Enterococcus species or other Gram-positive infections. Twelve patients developed thrombocytopenia (low platelet counts) during their course of treatment, although in seven patients platelet counts recovered before discontinuation. Thrombocytopenia is a known complication of burn injury (Shankar, Amin and Gamelli 2002), and may not have been related linezolid administration. However, in nine patients thrombocytopenia persisted for more than 9 days after therapy, and six of these patients succumbed to sepsis. No deaths were attributed to Gram-positive infection. As persistent low platelet count is thought to be a predictor of sepsis and death in patients with severe burns (Housinger, Brinkerhoff and Warden 1993), any dose increase should be made cautiously and the patient closely monitored for adverse effects.

Changing the method of administration of linezolid rather than the total daily dose, has the potential to alter the $\text{AUC}_{0-24}/\text{MIC}$ and $\%\text{T>MIC}$. One option would be the administration of linezolid by continuous infusion. This method was first reported in 2002 in a rabbit endocarditis model (Jacqueline et al.). Comparing an intravenous dose equivalent to 10mg/kg as an intermittent infusion every twelve hours, with 20mg/kg continuously over 24 hours and
40mg/kg continuously over 24 hours, in vivo activities were tested against three strains of S. aureus. With the intermittent infusion in vivo, linezolid had a bacteriostatic effect, but when the same total daily dose was given as a continuous infusion, a bactericidal effect was noted. Continuous infusion offered no benefit to linezolid in vitro in its activity against the three strains of MRSA tested.

One study (Adembri et al. 2008) has compared the use of intermittent (600mg twelve hourly) and continuous infusion (1,200mg/day) linezolid in sixteen critically ill patients. Pathogens isolated mainly had MICs of 2mg/L, although some were 1mg/L. Two out of the eight patients in each group died, with clinical success being recorded in the other patients. One patient in the continuous infusion group had thrombocytopenia before the linezolid commenced, which became severe during treatment. However blood counts returned to normal on the resolution of sepsis. An AUC/MIC(2mg) ratio of at least 80 was achieved in five out eight patients receiving intermittent infusion, and in seven of the eight on continuous infusion. A T>MIC(2mg) of at least 85% was measured in 3/8 and 8/8 for the two groups respectively. This led the authors to conclude that according to PK/PD parameters, continuous infusion has theoretical advantages over intermittent infusion in this population of patients. Further studies with a larger number of patients are required to determine whether there is any clinical benefit and a change to this method of administration as routine practice cannot yet be recommended. There is also some evidence to suggest that lower Cmax/MIC ratios, which will occur with continuous infusion, may increase the risk of emergence of resistance (Louie et al. 2008). Moreover, it can be seen from Table 5.7 that in patients with burns there is a risk of a steady-state serum concentrations of less than 4mg/L even at a dose of 1,800mg/24 hours, and therefore a T>MIC of 0%.

For future intermittent dosing, linezolid should be given over two hours, rather than thirty minutes, which is within the product license. This may increase the chance of therapeutic success. As the longest half-life measured in this study was almost ten hours, samples should ideally not be taken until at least 48 hours after the start of therapy. Samples may be taken four hours after the start
of the dose (once the distribution phase is complete) and then again after at least eight hours.

There is insufficient evidence to recommend that the standard starting dose of linezolid should be higher than 600mg every twelve hours in patients with major burns. However in those with abnormally high creatinine clearance measurements, a dose of 600mg every eight hours may be considered. The decision as to whether this dose should be used would depend on the age and weight of the patient, and on clinical state including the severity of the infection and platelet count.

5.6. Conclusions

This is the only study of the steady-state pharmacokinetics of linezolid in patients with major burns. It indicates the pharmacokinetics of linezolid may be altered in this population. Additionally, the manufacturer’s recommended dose of linezolid, 600mg twelve-hourly, may result in sub-therapeutic serum concentrations in some patients. Whilst the dose of 600mg twelve-hourly should remain the standard, a starting dose of 600mg every eight hours may be considered in severely ill younger adults who have evidence of a significant hypermetabolic response. Doses should be administered over two hours to increase the likelihood of therapeutic success.

The main limitation of this study was the low number of patients recruited to it. Data should therefore continue to be collected on burned patients receiving linezolid both to adjust serum concentrations as part of clinical care, and for future analysis. However, further studies are required to confirm the best marker of efficacy of linezolid. Based on the current evidence it is now recommended that serum concentrations should be adjusted to achieve a 24-hour area under serum concentration/time curve (AUC$_{0-24}$/MIC) ratio of greater than 80 and / or serum concentrations remaining above the MIC for the whole dose interval (T > MIC of 100%), with the latter being a more practical target. Measurement of the MIC$_{90}$ of the infective organism should be used to determine the target concentration, but where this is not known a concentration of 4mg/L should be adopted. Whilst ideally the T>MIC should be 100%, the
benefits of an increase above the recommended dose of 600mg twelve-hourly need to be balanced against the risks of adverse effects on an individual patient basis. Serum concentrations should ideally be measured at least 48 hours after the start of treatment; at four hours after the start of administration of the dose, and then after a further four or more hours.

Altering the mode of administration, such as to continuous infusion, may be a future strategy to increase the AUC$_{0-24}$/MIC and T$>$MIC, but clinical studies of large numbers of patients are required, before this can be recommended the method of choice. If such a method is shown to be more efficacious, pharmacokinetic data may be applied to develop dosing guidelines in patients with severe burns.

5.7. Recommendations

A linezolid dose of 600mg (administered over two hours) every twelve hours should remain as the standard dose in patients with severe burns. A starting dose of 600mg every eight hours may, however, be considered in severely ill younger adults who have evidence of a significant hypermetabolic response.

Ideally doses should be adjusted to achieve linezolid serum concentrations above the MIC for 100% of the dose interval, but the potential benefit of administration of doses over 600mg every twelve hours should be balanced against the increased risk of adverse drug effects. Serum concentrations should be measured at least 48 hours after the start of treatment; at four hours after the start of administration of the dose, and then after a further four or more hours. Measurement of the MIC$_{90}$ of the infective organism should be used to determine the target concentration, but where this is not known a concentration of 4mg/L should be adopted.

These recommendations have been made to the multidisciplinary burns team at the Queen Victoria Hospital and the proposals have been agreed for all future treatment of patients with major burns. Adoption of these recommendations may reduce morbidity and mortality of severely burned patients with multi-resistant Gram-positive infections.
Chapter 6. Colistin

6.1. Introduction

Colistin, also known as polymyxin E, is a polymyxin antibiotic, which is licensed for the treatment of severe systemic or localised infections such as septicaemia or respiratory infections caused by Gram-negative bacteria (Pharmax 2001b). In practice, it is generally reserved for the treatment of infections caused by Gram-negative organisms that are resistant to all other antibiotics.

It is active in vitro against many clinically important Gram-negative bacilli, with the notable exceptions of Proteus spp and some Shigella species. It is not active against Gram-positive bacteria, Gram-negative cocci and most fungi (Schwartz et al. 1959 /60).

Colistin sulphate, also known as polymyxin E, is a multicomponent polypeptide antibiotic first isolated from Bacillus colistinus in 1950 (Koyama et al. 1950). Although it was a potent antimicrobial agent it exhibited a range of toxic side effects. Consequently in the early 1960s colistimethate sodium (also known as colistimethate sodium and colistin methanesulphonate) was developed (Edgar and Dickinson 1962). It was formulated to be as active as colistin, but less toxic, making it the drug of choice for parenteral administration. In the 1970s, the demand for the drug diminished as the use of antibiotics such as aminoglycosides, which were thought to be even less toxic, became more widespread. However, in the 1990s, its use increased again because of Gram-negative bacteria becoming resistant to the newer antibiotics (Evans, Feola and Rapp 1999).

Colistin has a molecular weight of approximately 1200 Da. Its basic structure comprises a polycationic peptide ring containing eight to ten amino acids with a high percentage of 2,4-diaminobutyric acid (Dab) residues. It also has a fatty acid side chain (either 6-methyloctanoic acid or 6-methylheptanoic acid) attached to the peptide ring, usually through an amide linkage. The positively charged Dab molecules and the fatty acid tail make colistin amphipathic, which
allows it to distribute well into both aqueous and non-aqueous environments (Evans 1999). Colistimethate sodium is formed from colistin sulphate by treating the primary amine groups of $\alpha,\gamma$-diaminobutyric acid residues in colistin with formaldehyde followed by sodium bisulphite (Li et al. 2002). The resulting product is a mixture of the mono-, di-, tri-, tetra- and penta-substituted compounds. Many components have been isolated from colistin, with the two main components being colistin A and colistin B (Orwa et al. 2001). The proportion of these two differ between the different brands and different batches (Decolin et al. 1997).

6.1.1. Mode of action and resistance of colistin

Colistin is bactericidal, and in susceptible Gram-negative bacteria, polymyxins have a detergent-like action, interfering with the structure and function of the cell membrane. It is thought to interact with the lipopolysaccharide (LPS) of the outer membrane causing it to become porous, so affecting the osmotic integrity of the cell. As a result, intracellular constituents such as potassium ions, nucleotides and proteins, leak out, causing cell death (Evans, Feola and Rapp 1999; Hancock and Chapple 1999).

Initial binding to the outer membrane takes place when the cationic portion of colistin displaces calcium and magnesium ions that normally stabilise LPS molecules in the outer leaflet of the bacterial outer membrane (Leive 1974; Schindler and Osborn 1979). Additional complexing with LPS is facilitated by hydrophobic interactions between the lipid A portion of LPS and the fatty acid of colistin (Morrison and Jacobs 1976). Entry into the cell is thought not to be necessary as polymyxin B, covalently attached to agarose beads, has been shown to retain the ability to alter membrane permeability and inhibit bacterial respiration (LaPorte, Rosenthal and Storm 1977).

The polymyxins are unique among antibiotics in that they bind tightly to endotoxins, (toxin released when microorganisms are broken down or die) and block their activity (Gudmendsson and Craig 1986). However, the potential benefit of this in Gram-negative sepsis or endotoxin-mediated shock has never been shown in human trials.
Resistance to colistin can easily be induced in vitro, but has not been widely documented in clinical practice (Evans, Feola and Rapp 1999; Littlewood et al. 2000). However Li et al (2001b) reported a resistance rate of approximately 19% against *Pseudomonas aeruginosa* in their population of patients with cystic fibrosis. The authors suggest that the high incidence may have been due to the frequent use of inhaled colistin in these patients, and that the reports of a low incidence of resistance preceded the widespread use of colistin by this method of administration. The mechanism of resistance is unclear, although it was suggested that it was related to over-expression of OprH, an outer membrane protein (Nicas and Hancock 1980; Young et al. 1992). More recently it has been proposed that resistance is due to modification of lipid A of LPS, mediated by the novel two-component regulatory system ParR-ParS when colistin levels are sub-inhibitory (Fernandez et al. 2010).

**6.1.2. Colistin indications**

Colistimethate sodium is indicated to be administered either by inhalation for the treatment of *P.aeruginosa* lung infection in patients with cystic fibrosis, or by intravenous administration against serious infections caused by Gram negative bacteria, when more commonly used systemic antibacterial agents may be contra-indicated or may be ineffective because of bacterial resistance (Forest_Laboratories 2010).

**6.1.3. Dose, administration and monitoring of colistin**

In the UK, the brand of colistin sulphomethate is Colomycin®, which has the dose expressed in units. The standard adult dose in 2002, the time of the commencement of this study, was 2,000,000 units (2MU) administered as an intravenous infusion over 30 minutes every eight hours (Pharmax 2001b). A dose reduction was recommended in patients with renal impairment. The licensed dose at the commencement of the study in 2002 is shown in table 6.1.

The table demonstrates that there was some inconsistency with the UK dosage. A child of 61kg with normal renal function would have received a dose of 2 MU
three times a day. If the child weighed 1kg less, the total daily dose would have been $60 \times 50,000 = 3$ MU ie 1MU three times a day.

<table>
<thead>
<tr>
<th>Creatinine Clearance (ml/min)</th>
<th>Adult dosage (and children over 60kg)</th>
<th>Children’s dosage (under 60kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 72</td>
<td>2 MU every 8 hours</td>
<td>50,000 units / kg/ day in three divided doses</td>
</tr>
<tr>
<td>20 – 72</td>
<td>1-2 MU every 8 hours</td>
<td>12,500 – 16,000 units / kg every 8 hours</td>
</tr>
<tr>
<td>10 – 22</td>
<td>1 MU every 12 – 18 hours</td>
<td>12,500 units / kg every 12 – 18 hours</td>
</tr>
<tr>
<td>&lt;10</td>
<td>1 MU every 18 – 24 hours</td>
<td>8,000 units / kg every 18 – 24 hours</td>
</tr>
</tbody>
</table>

Table 6.1 Dose of colistin sulphomethate (Colomycin®) licensed in the UK in 2002 (Pharmax 2001b)

Dosage guidelines have since been updated (Table 6.2) and the inconsistency addressed.

<table>
<thead>
<tr>
<th>Renal function</th>
<th>Creatinine Clearance (ml/min)</th>
<th>Dosage (over 60kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&gt; 50</td>
<td>1-2 MU every eight hours</td>
</tr>
<tr>
<td>Mild impairment</td>
<td>20 to 50</td>
<td>1-2 MU every 8 hours</td>
</tr>
<tr>
<td>Moderate impairment</td>
<td>10 - 20</td>
<td>1 MU every 12 - 18 hours</td>
</tr>
<tr>
<td>Severe impairment</td>
<td>&lt;10</td>
<td>1 MU every 18 – 24 hours</td>
</tr>
</tbody>
</table>

Table 6.2 Dose of colistimethate sodium (Colomycin®) licensed in the UK for adults and children in 2010 (Forest_Laboratories 2010)

For patients under 60kg, it is recommended that the dose is now 50,000 units/kg/day to a maximum of 75,000 units/kg/day, given in three divided doses.

In the US, Coly-Mycin M® is the licensed brand and current dosage recommendations have altered only slightly since 2001 (Table 6.3). Vials are labelled as containing 150mg base activity per vial, which is approximately
equivalent to 400mg or 5MU of colistin sulphomethate (Pharmax 1996; Evans, Feola and Rapp 1999). One unit of colistin is defined as the minimum amount needed to inhibit the growth of the National Institute of Hospitals, Japan standard strain of *Escherichia coli* in 1ml of culture broth at pH 7.2 (Pharmax 1996). The recommended doses of this brand are approximately twice that of Colomycin®. Because of these differences, the brand name will be stated in the rest of this chapter where known. Additionally there are other manufacturers of colistimethate sodium worldwide (Li *et al.* 2006b), which adds to the confusion when interpreting data from publications.

<table>
<thead>
<tr>
<th>Degree of renal impairment (plasma creatinine converted from mg/dL to micromol/L)</th>
<th>Dose (base activity in mg)</th>
<th>Approximate dose in MU (based on 70kg patient)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (60-110)</td>
<td>5.0mg / kg / day into 2 to 4 equal divided doses</td>
<td>5MU every 12 hours</td>
</tr>
<tr>
<td>Mild (115 - 130)</td>
<td>2.5 – 3.8 mg / kg / day in 2 divided doses</td>
<td>2.5 to 4MU every 12 hours</td>
</tr>
<tr>
<td>Moderate (140-220)</td>
<td>2.5mg/kg day in 1 or 2 divided doses</td>
<td>2.5MU every 12 hours</td>
</tr>
<tr>
<td>Considerable (230-350)</td>
<td>1.5mg/kg every 36 hours</td>
<td>3MU every 36 hours</td>
</tr>
</tbody>
</table>

*Table 6.3 Dose of colistin (Coly-Mycin M®) in the US in 2010 adapted from (Monarch 2009)*

With Colomycin® the recommended serum concentration target of 10 to 15mg/L has been unchanged since 2002. The British National Formulary states that this should be taken approximately 30 minutes after the end of the infusion (BNF 2009). There are no recommendations for serum monitoring with Colymycin M®.

### 6.1.4. Colistin toxicity

Renal toxicity and neurotoxicity are the main adverse effects associated with colistimethate sodium use (Pharmax 2001b)

Nephrotoxicity is thought to be due to colistimethate sodium causing an increase in permeability of tubular epithelial cell membranes, resulting in an increased influx of cations, anions and water, leading to cell swelling and lysis
measured acute toxicity of both forms of colistin in mice and found that colistimethate sodium (Colomycin®) (LD50 > 550mg/kg) was much less toxic than the sulphate (LD50 10mg/kg).

Koch-Wese, Sidel and Federman (1970) monitored 288 patients receiving 317 courses of sodium colistimethate therapy (Coly-mycin M®). The most common infections were pneumonia (28.7%), septicaemia (26.8%), pyelonephritis (20.5%) and wound infections (12.3%). The drug was administered by intramuscular injection with total daily doses ranging from less than 99mg/day to over 299mg/day. Assuming this refers to colistin base, the equivalent dose in units would be approximately <3 to >10MU/day. Colistin caused adverse effects in 72 (25.1%) of the 288 patients and renal effects were most common during 64 (20.2%) of the 317 courses. Of the 72 patients with adverse effects 44.4% died, compared with 41.7% of the patients who did not experience adverse effects. Of the 32 deaths that followed adverse effects, 22 had post-mortems performed. Thirteen of these patients had evidence to suggest that the adverse effects contributed significantly to their death. It was difficult to be certain of the cause of death because of the complexity of the clinical situation and the severity of underlying diseases.

Renal toxicity is thought to be dose-dependent, so occurs most often when higher than recommended doses are used in patients with normal renal function, when the dose is not reduced in patients with renal failure, or when colistin is used with other nephrotoxic drugs. The effect is usually reversible if colistin is discontinued, with renal function usually returning to baseline in three to nine weeks (Price 1970). The polymyxins may cause acute tubular necrosis manifested by albumunuria, cellular casts, reduced urine output and rising serum blood urea, nitrogen and creatinine (Wolinsky and Hines 1962; Brown, Dorman and Roy 1970; Price and Graham 1970).

In a case report (Brown, Dorman and Roy 1970), a ten-month boy was accidentally given over fifteen times the recommended dose of colistimethate. Several hours after the dose was given, the infant became flushed, but showed
no other adverse effects. His blood was then collected for microbiological serum assay and was estimated to be 320 mg/L. The infant passed a small amount of urine in the following 24 hours and then became anuric for 36 hours. No neurological adverse effects were noted. Initial treatment was peritoneal dialysis, which was ineffective. Exchange transfusion followed, which lowered serum colistin levels and blood urea concentration. Six weeks after the anuria, renal function had returned to normal.

There were no signs of neurotoxicity throughout the episode with the ten-month old, although the overall incidence has been reported as 7.3% (Koch-Weser, Sidel and Federman 1970). Symptoms begin with restlessness and distal paraesthesia, followed by ptosis, diplopia, dysphagia, dysphonia, generalised weakness, ataxia and areflexia (Wolinsky and Hines 1962; Lindesmith et al. 1967). Onset of signs of neurotoxicity may occur within one hour of the first dose, or after several days of therapy. Patients receiving other neuromuscular blocking agents are particularly at risk (Evans, Feola and Rapp 1999) but the effects are usually reversible (Bosso et al. 1991; Conway et al. 1995).

It has been suggested (Conway et al. 1997) that the high incidence of toxicity reported with colistin is as a result of inappropriate patient selection, higher-than-recommended doses and inappropriate monitoring. However, in a study by Southern et al (1993), 22 cystic fibrosis patients received intravenous colistin at a daily dose of 150% of that recommended by the manufacturers. There was no evidence of neurotoxicity or nephrotoxicity in any patients.

Conway et al (1995) studied the adverse effects of 71 adult patients with cystic fibrosis, who received intravenous colistimethate sodium 2MU three times a day, either alone (n=36) or in combination with a second anti-pseudomonal antibiotic (n = 35). Five patients withdrew from the monotherapy group, and four from the duotherapy group. Only two of these might have been drug-related withdrawals, both occurring in the monotherapy group. One of these patients had severe weakness and dizziness, the other a skin rash.
Fever, rash, allergic reactions and pain at the injection site have also been reported with the polymyxins (Koch-Weser, Sidel and Federman 1970; Evans, Feola and Rapp 1999).

6.1.5. Pharmacokinetics

To measure the concentration of colistin in serum, studies (Boger and Gavin 1962; Leroy et al. 1989) first used the agar plate diffusion method with *Bordetella bronchiseptica* 4617 as the test organism, a modification of the U.S. Food and Drug Administration method for the assay of polymyxin. This method is unable to distinguish between the sulphate and sulphomethate forms (Barnett, Bushby and Wilkinson 1964), and also lacks specificity, particularly when samples contain other antibiotics that are active against the test strain. More recently methods for the HPLC analysis have been published (Le Brun, De Graaf and Vinks 2000; Li et al. 2001a; Reed et al. 2001; Li et al. 2002), as discussed in Chapter 3, Section 3.8 but only the methods by Li et al. (2001a and 2002) distinguish between the two forms of colistin.

6.1.5.1. Pharmacokinetics of colistin in healthy subjects

Colistimethate sodium can be administered by intravenous, intramuscular, oral, topical or aerosol routes, with only the parenteral routes consistently resulting in significant systemic absorption (Bergan and Fuglesang 1982; Jensen, Pedersen and Garne 1987; Fekety 1990). Absorption following administration by inhalation systemic is reported to be less than 0.2mg/L following a dose of 2MU (Ratjen, Beier and Grasemann 2006).

As soon as the injection is reconstituted, colistimethate starts to hydrolyse to colistin base which is thought to be an active metabolite (Barnett, Bushby and Wilkinson 1964). Some of the different compounds making up colistimethate sodium may not fully hydrolyse, and hydrolysis of the compounds may be at different rates. Colistin is reversibly bound to body tissues, but binding is not thought to occur with the sulphomethate form (Martindale 2002). It penetrates into most tissues, pleura and joints, but is not thought to readily diffuse across
the blood-brain barrier (Barnett, Bushby and Wilkinson 1964). Protein binding of colistin is thought to be low (Dollery 1991).

In a study of 10 healthy volunteers (Froman, Gross and Curatola 1970), a single intravenous dose of 150mg of Coly-mycin M® (approximately 5MU) administered over a frequency not stated, resulted in a mean peak serum concentration 10 minutes after administration of 18mg/L. The serum half-life initially was about 1.5 hours, and after 4 hours serum levels had declined to about 2mg/L. The authors concluded that intravenous injection of sodium colistimethate produces effective inhibitory blood concentrations of antibiotic, although the reasoning for this statement was not put forward.

Elimination is thought to be mainly by renal excretion, with approximately 75% of colistin excreted via the kidneys 24 hours after a single dose (Froman, Gross and Curatola 1970). The excretion of the remaining colistin is not known, but it is has been suggested that it is inactivated slowly in the tissues (Pharmax 1996). The elimination of colistin is reduced in subjects with impaired creatinine levels, resulting in increased serum concentrations (Höffler and Scheler 1964).

6.1.5.2. Pharmacokinetics of colistin in patients without burns

Lower peak serum concentrations of colistin have been reported in patient studies compared with those in healthy volunteers. Eight patients, aged 25 to 69 years with systemic infections due to P.aeruginosa received an intravenous dose of 2 to 2.5mg/kg Coly-mycin M® (approximately 5MU) every twelve hours (Baines and Rifkind 1964). Peak levels (immediately following a 20 to 30 minute infusion) taken on days 1 to 4 of treatment ranged from 6 to 15.5mg/L (mean 9.6mg/L). Higher concentrations were generally noted in patients with impaired renal function (Table 6.4)
Table 6.4 Serum concentrations of colistimethate sodium following administration of 2 to 2.5mg/kg (approximately 5MU) over 20 to 30 minutes twelve-hourly adapted from (Baines and Rifkind 1964)

<table>
<thead>
<tr>
<th>Case No</th>
<th>Immediately</th>
<th>1</th>
<th>4</th>
<th>8 Before therapy</th>
<th>After therapy**</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10.0</td>
<td>3.9</td>
<td>1.9</td>
<td>&lt;0.5</td>
<td>36</td>
</tr>
<tr>
<td>2</td>
<td>6.3</td>
<td>3.0</td>
<td>0.8</td>
<td>.....</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>6.0</td>
<td>5.6</td>
<td>1.5</td>
<td>&lt;1</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>6.7</td>
<td>6.5</td>
<td>.....</td>
<td>.....</td>
<td>127</td>
</tr>
<tr>
<td>5*</td>
<td>15.5</td>
<td>14.3</td>
<td>7.5</td>
<td>3.8</td>
<td>63</td>
</tr>
<tr>
<td>6</td>
<td>8.4</td>
<td>7.0</td>
<td>3.8</td>
<td>.....</td>
<td>25</td>
</tr>
<tr>
<td>7</td>
<td>10.8</td>
<td>9.8</td>
<td>3.8</td>
<td>2.6</td>
<td>75</td>
</tr>
<tr>
<td>8*</td>
<td>12.8</td>
<td>6.8</td>
<td>.....</td>
<td>.....</td>
<td>12</td>
</tr>
</tbody>
</table>

* Died
** Length of treatment 8 – 14 days

MacKay and Kaye (1964) compared serum concentrations of Coly-mycin M® in four patients with normal renal function, with eighteen patients with differing degrees of renal impairment following a single intramuscular injection of colistimethate sodium equivalent to either 75 or 150mg colistin base. Serum concentrations were determined by microbiological techniques, which were different from the standard using B. bronchiseptica. (Escherichia coli were used in most cases, but where other antibiotics were being used in addition to colistin, Aerobacter aerogenes was used, as it grew in broth containing 100mcg/L of penicillin, streptomycin, chloramphenicol and tetracycline.) This meant that concentrations were recorded as <3.1mg/L, 3.1 mg/L, 6.3mg/L, 12.5mg/L and 25.0mg/L. Peak concentrations, one hour after injection, in all groups were either 12.5 or 6.3mg/L. There was little difference between the levels of patients with normal renal function (urea clearance of 80% of normal or higher) and patients with a urea clearance of between 40 and 68% of normal, with concentrations dropping below 3.1mg/L by 24 hours in all but one from each group. In patients with poorer renal function, the length of time detectable colistin concentrations were maintained appeared to be related to the degree of
renal impairment. Haemodialysis using the Kolff twin-coil artificial kidney did not remove colistin. The two patients with anuria in acute renal failure still had serum concentrations of 12.5mg/L four days after the administration of colistin.

Most of the more recent work on the pharmacokinetics of colistin has focussed on patients with cystic fibrosis (CF) (Kearns, Hilman and Wilson 1982; Prandota 1988; Lindsay and Bosso 1993). As with patients with burn injury, many drugs in patients with CF have altered pharmacokinetic parameters when compared with healthy individuals. Most commonly these are larger than expected volumes of distribution, and increased renal and non-renal clearance.

In a UK study Conway et al (1997) administered a dose of 2MU of colistimethate sodium every eight hours to patients chronically colonised with colistin-sensitive P.aeruginosa, who were experiencing an acute respiratory exacerbation. Serum concentrations were measured using a microbiological assay and the mean peak concentration was 12.3mg/L and trough 2.3mg/L from 23 pairs of blood samples. Eleven patients had peak concentrations below the 10 – 15mg/L, which the authors state is the optimal ranged based on the work by Frohman, Gross and Curatola (1970) and is that recommended in the summary of product characteristics for Colomycin® (Forest_Laboratories 2010). Four patients had peak levels of between 9 and 10mg/L. Seven had peak levels of less than 9mg/L, the two lowest being 5.1 and 5.2 mg/L. One patient had very high levels (>25mg/L), but experienced no toxic effects. All patients showed clinical improvement and resolution of their acute respiratory exacerbations. The authors suggest that greater therapeutic efficacy might result from individual adjustment of colistin according to serum levels, but they are not routinely available.

In a U.S. study (Reed et al. 2001), 31 patients with cystic fibrosis (age 14 – 53) experiencing acute pulmonary exacerbations patients were given colistimethate sodium in doses up to 100mg of colistin base (approximately 3MU) every eight hours over 30 minutes. Colistin serum concentrations were measured by HPLC assay. Following the first dose, there were wide-ranging peak serum concentrations of 12.9 – 32.3mg/L (mean 21.4mg/L), which were notably higher than that reported by Conway et al, most likely due to the higher doses used,
and/or the assay method used (Table 6.5). At steady-state, the mean peak concentration was slightly higher (23mg/L). Eight-hour trough levels also varied widely after the first dose (range 0.7 – 7mg/L) and at steady state (0 – 21.7mg/L). These variations can be partly explained by the variation in dosing range.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>First dose (n=30)</th>
<th>Steady-state (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (mg/L)</td>
<td>21.4 ± 5</td>
<td>23 ± 6</td>
</tr>
<tr>
<td>$C_{\text{min8h}}$ (mg/L)</td>
<td>2.8 ± 1.8</td>
<td>4.5 ± 4</td>
</tr>
<tr>
<td>$t\frac{1}{2}$ (h)</td>
<td>3.4 ± 1.4</td>
<td>3.5 ± 1</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>4.4 ± 1.7</td>
<td>4.6 ± 1.4</td>
</tr>
<tr>
<td>$V_{\text{dss}}$ (L/kg)</td>
<td>0.09 ± 0.02</td>
<td>0.09 ± 0.03</td>
</tr>
<tr>
<td>$\text{Cl}$ (ml/min/kg)</td>
<td>0.35 ± 0.09</td>
<td>0.34 ± 0.09</td>
</tr>
<tr>
<td>$\text{Clr}$ (ml/min/kg)</td>
<td>0.24 ± 0.15</td>
<td>-</td>
</tr>
<tr>
<td>$\text{Clr}:\text{Cl}$ ratio</td>
<td>0.62 ± 0.32*</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 6.5 First-dose and steady-state pharmacokinetics of colistin (base activity) in 31 patients with cystic fibrosis adapted from Reed et al (2001).

* n=13 $C_{\text{max}}$ = maximum plasma colistin concentration, $C_{\text{min8h}}$ (8-hour trough colistin plasma concentration), $t\frac{1}{2}$ = elimination half-life, MRT = mean residence time, $V_{\text{dss}}$ = steady-state volume of distribution, $\text{Cl}$ = body clearance, $\text{Clr}$ = renal clearance

Colistin was primarily cleared though the kidney, but approximately 40% was cleared by non-renal pathways. It was thought that a significant amount was likely to have been excreted in the sputum.

6.1.5.3. Pharmacokinetic studies of colistin in patients with burns

Villarreal et al (2000) described the use of colistimethate sodium against $P.\text{aeruginosa}$ measured in five paediatric burn patients. Serum concentrations were determined by the standard microbiological assay. Steady state concentrations were reported to be 100mcg/ml for four patients, and 1mcg/ml for the other patient, although the report does not indicate what steady-state concentrations these are. Efficacious and safe concentrations were deemed to
be 100mcg/ml or less. These values vary widely from previous pharmacokinetic studies in patients without burns, who usually have peak serum concentrations of no more than 25mcg/ml.

6.1.6. Pharmacodynamics of colistin

Research up to 2002 indicated that both colistin and colistimethate sodium had antimicrobial activity.

Barnett, Bushby and Wilkinson (1964) measured the MICs of both forms (sulphate and sulphomethate) and found lower MICs against *P. aeruginosa* for the sulphate (Table 6.6).

<table>
<thead>
<tr>
<th></th>
<th>MIC 90 (mg/L) against <em>P. aeruginosa</em></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nutrient Broth</td>
</tr>
<tr>
<td>Colistin sulphate</td>
<td>0.46</td>
</tr>
<tr>
<td>Colistimethate sodium</td>
<td>1.97</td>
</tr>
</tbody>
</table>

*Table 6.6 In vitro activity of the forms of colistin adapted from Barnett, Bushby and Wilkinson (1964)*

The authors of this study highlighted that the activity of the sulphomethate may have been overestimated because of breakdown to the more active sulphate form during the relatively long 18-hour incubation period. This possibility was tested by increasing the number of organisms so that growth in the nutrient broth in the absence of antibiotics was visible after 3 hours incubation. Activity of the sulphomethate increased considerably over a 24 hour period. Additional evidence that the sulphomethate forms of the polymyxins were much less active was then gained by two further experiments. Firstly activities were measured against *Klebsiella pneumoniae* which showed that for colistimethate sodium, the concentration needed to kill 50% of the organisms was 19.7mg/L after 30 minutes, 5.6mg/L after 1 hour and 2.2mg/L after three hours. (This not only shows that colistimethate is less active, it also demonstrated the degradation of colistimethate to sulphate.) In the second experiment, antibiotics at those concentrations found in blood were incubated at 37°C for 1 hour and 3 hours
before the antibacterial activities were measured against *K. pneumoniae*. At 1 hour, the ED$_{50}$ of colistimethate sodium was 1.2mg/L and at three hours, it was 0.44mg/L.

The *in vitro* activity of colistin sulphotemate (Colomycin$^{\text{®}}$) against clinical isolates of two Gram-negative bacteria, commonly pathogenic in patients with burns, measured by the agar dilution technique is shown in Table 6.7 (Catchpole *et al.* 1997). The MICs are considerably higher than those measured by Barnett, Bushby and Wilkinson (1964). This could be due to different techniques used for measuring the MIC, or because of an increase in resistance over the years.

<table>
<thead>
<tr>
<th>Organism (no. of strains)</th>
<th>MIC$_{50}$ (mg/L)</th>
<th>MIC$_{90}$ (mg/L)</th>
<th>Range</th>
<th>% susceptible at recommended BSAC breakpoint of 4mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Ps. aeruginosa</em> (94)</td>
<td>2</td>
<td>4</td>
<td>0.5 - 32</td>
<td>97%</td>
</tr>
<tr>
<td><em>Acinetobacter</em> species (23)</td>
<td>1</td>
<td>2</td>
<td>1 - 128</td>
<td>96%</td>
</tr>
</tbody>
</table>

*Table 6.7 In vitro activity of colistimethate sodium adapted from Catchpole et al (1997)*

Li *et al* (2001b) demonstrated that colistimethate sodium (Coly-Mycin$^{\text{®}}$) had a lower overall activity than colistin sulphate against 23 strains of *P. aeruginosa* isolated from patients with cystic fibrosis with a mean MIC of 7.1mg/L versus 3.1mg/L respectively for all susceptible strains tested (p<0.05) (Li *et al.* 2001b). The authors state that the MICs in this Australian study may vary from those given by Catchpole *et al.* (1997) because of differences in the compounds making up the colistimethate sodium between manufacturers’ preparations. (Colistin preparations are produced from the fermentation of *Bacillus colistinus* (Pharmax 1996) and therefore only slight differences in the manufacturing process may affect activity.)

Colistin has been shown to exhibit rapid concentration-dependent killing, but despite the antibiotic being in use for fifty years, the exact marker of efficacy is not known. Li *et al* (2001b) found *in vitro* that at a concentration of 64 x MIC colistin sulphate completely eradicated *P. aeruginosa* in five minutes. The rate
of killing decreased as the concentration decreased, but even a concentration of 1 x MIC bacteria were undetectable after four hours. Complete eradication only failed in 0.5 x MIC. With colistimethate sodium, killing was less rapid, with 64 x MIC taking one hour for complete eradication, and 16 x MIC taking four hours. Concentrations of 8 x MIC and lower failed to eradicate bacteria from clinical isolates at 24 hours. These findings were consistent with that of MacGowan et al (1999), which showed a more rapid killing by colistimethate sodium at 5mg/L than 0.5mg/L. The study by Li et al (2001b) also showed a significant post-antibiotic effect (> 1 hour) for both colistin and colistimethate sodium but only at the highest concentrations studied. The findings from this study led the authors to propose that higher total daily doses of colistimethate sodium may be required in patients with cystic fibrosis. Because of the dose-dependent killing, it is possible that the total daily dose may be better administered as a single dose, as has been the changed practice of dosing with aminoglycosides.

The UK manufacturers of Colomycin® recommend that blood concentrations should be measured (particularly for patients with renal impairment, neonates and patients with cystic fibrosis) and that 10 to 15mg/L “should be adequate” for most infection (Beaco 2010; Forest_Laboratories 2010; Profile_Pharma 2010). Personal communication with Forest Laboratories confirmed that this should be a blood sample taken one to three hours after the commencement of administration, after at least one day of treatment. The British National Formulary (2010) also recommends that for patients with cystic fibrosis and renal impairment, a “peak” plasma concentration is measured approximately 30 minutes after the end of the infusion or injection and that this should be 10 to 15mg/L. These recommendations appear to be made based on the study, previously discussed, by Froman, Gross and Curatola (1970), where a mean peak level of 18mg/L was measured ten minutes after administration of a single dose. From examining their data of serum colistin concentration versus time, it appears that the mean blood level 30 minutes after administration was approximately 10mg/L, which may be the reason for the recommendation. The authors stated that intravenous injection of sodium colistimethate produces effective inhibiting blood levels of antibiotic.
Two studies, already discussed, have related patient outcome with serum concentrations. Firstly (Baines and Rifkind 1964) in the study of eight patients, bacteriological cure was achieved in five patients. Of the three patients where *P. aeruginosa* was not eradicated, two died as a result of their infection. These patients all had peak serum concentrations above the mean of 9.6mg/L.

Secondly, in the study of five paediatric patients with burns (Villarreal *et al.* 2000), efficacious and safe concentrations were deemed to be 100mcg/ml or less, although no therapeutic outcome data were described.

In summary, at the time of commencement of this study in 2002, it appeared that colistimethate sodium was hydrolysed to colistin base in the body, with colistin being more active than the sulphomethate form. The drug was thought to exhibit concentration-dependent killing, but it was not clear what concentrations were required in practice to achieve maximum efficacy. The established microbiological method for the assay of colistin lacked specificity and was unable to distinguish between the two forms of colistin, or other antibiotics that are active against the test strain. This may in part explain why serum concentrations measured from older studies were inconsistent. A newer HPLC method could distinguish between the two forms of colistin (Li *et al.* 2001a; Li *et al.* 2002). If reproducible, this would be useful for calculating pharmacokinetic parameters of each form, but how these were applied to clinical practice had not yet been established. However, as described in Chapter 3, Section 3.8 this assay is not straight forward and is very difficult to replicate.

6.2. Aims and objectives

As outlined in Chapter 1, Section 1.11, the aims of this study were to investigate the pharmacokinetic parameters of antibiotics when administered to patients with major burns and to produce dosing guidelines for the use of these antibiotics.
Objectives were:

- To measure the serum concentrations of colistin in adults with major burns (>15% total body surface area) receiving this antibiotic for treatment of severe infections.
- To compare the serum concentrations with those required to treat likely infections.
- To calculate pharmacokinetic parameters such as volume of distribution, clearance and elimination half-life.
- To compare pharmacokinetic parameters calculated in this study of severely burned patients with other populations.
- To investigate the influence of patient factors on the serum concentrations and pharmacokinetic parameters.
- To produce dosage guidelines for the use of colistin in adults with major burns.

6.3. Method

The methodology for the pharmacokinetic study of colistin together with the other antibiotics is described in Chapter 3.

For the colistin pharmacokinetic study, a peak concentration of 10 to 15mg/L was selected as the marker of efficacy, as this complies with the product license recommendations in the UK. Studies since 2002 will be reviewed in the discussion (Section 6.5.3) to determine whether this is still the best marker of efficacy.

Colistin was assayed by the microbiological method described in Section 3.8, as the recommendation of 10 to 15mg/L was made using this method. Additionally, the microbiological assay could be provided by an established service, so allowing prompt results in time to make alterations to patient therapy if necessary.
6.4. Results

One patient only was recruited to the study. One further patient was eligible, but difficulty contacting the next-of-kin excluded him due to lack of consent.

The patient who was recruited to the study was a 38 year old woman of Chinese descent, weighing 60kg. She had 70% total body surface area (TBSA) burns, thought to be due to a chemical burn, although this was never confirmed. She did not have an inhalation injury, but died 119 days after admission to the burns centre. Her age plus percentage burn was 108 (poor prognosis), and her ABSI score was 10 (severe threat to life).

At the time of sampling the patient had a serum creatinine concentration of 37 micromol/L, a creatinine clearance of 78ml/min and an albumin of less than 10g/L. She had 30% TBSA burn remaining when the infection was diagnosed.

Organisms identified at the time of her requiring treatment with colistin were *Pseudomonas* spp. (sensitive to colistin only) and *Acinetobacter* spp. (sensitive to colistin and meropenem) in the sputum and wound, and *Stenotrophomonas maltophilia* (sensitive to co-trimoxazole) in her sputum. Colistin was commenced as monotherapy and was given for 15 days. After seven days, the patient was also commenced on an eight-day course of flucloxacillin 2g every six hours, due to the isolation of *Staphylococcus aureus*.

The patient was commenced on the standard dose of colistin; 2MU every eight hours, given over 30 minutes. This resulted in predicted serum concentrations at one hour of 8.3mg/L. When the dose was increased to 2.5MU eight-hourly, peak serum concentrations in the one to three hour period were 9.8mg/L (Figure 6.1). Samples were taken on days 129 and 136 of treatment.
Figure 6.1 Serum concentrations of colistin for 2MU (set 1) and 2.5MU (set 2) given every eight hours

An intravenous dose of colistimethate sodium of 2MU (infused over 30 minutes) every eight hours resulted in subtherapeutic serum concentrations i.e. less than 10mg/L 30 minutes after the completion of infusion. The dose was increased to 2.5MU every eight hours, but the concentration was still sub-therapeutic.
Whilst the calculated clearance was the same for both doses, there were variations in the other calculated parameters (Table 6.8).

<table>
<thead>
<tr>
<th>Dose</th>
<th>Dosing interval</th>
<th>$C_{\text{max}}$ (mg/L)</th>
<th>$C_{\text{max}/}$ (mg/L/MU)</th>
<th>AUC$_{0-\infty}$ (mg/L.h)</th>
<th>$t_{1/2}$ (h)</th>
<th>V (L)</th>
<th>V (L/kg)</th>
<th>CL (L/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2MU</td>
<td>8 hourly</td>
<td>11.0</td>
<td>5.5</td>
<td>36</td>
<td>8.3</td>
<td>23</td>
<td>0.38</td>
<td>1.9</td>
</tr>
<tr>
<td>2.5MU</td>
<td>8 hourly</td>
<td>18.5</td>
<td>7.4</td>
<td>57</td>
<td>6.1</td>
<td>17</td>
<td>0.28</td>
<td>1.9</td>
</tr>
</tbody>
</table>

*Table 6.8 Colistin pharmacokinetic parameters for one patient at two different doses*
6.5. Discussion

6.5.1. Colistin serum concentrations

This is the first time that colistin pharmacokinetic parameters have been calculated for a patient with major burns. Two series of serum samples were collected from the one patient, at doses of 2MU and then 2.5MU eight-hourly. At the licensed dose of Colomycin® 2MU eight-hourly, serum concentrations were sub-therapeutic according to the recommendations of the product license, but despite the dose increase, concentrations were still less than the recommended 10 – 15 mg/L thirty minutes after the completion of infusion. This confirms the need to monitor serum concentrations in this group of patients and adjust doses accordingly in order to adhere to the product license. To have achieved therapeutic serum concentrations, it is likely that a dose of 3MU eight-hourly would have been required. Two papers (Markou et al. 2008; Plachouras et al. 2009) have shown that a dose of 3MU eight-hourly is generally well-tolerated in critically ill patients.

As expected, both the peak concentration measured immediately after the completion of the infusion and the area under the curve were greater with the higher dose.

David and Gill (2008) reported the use of intravenous colistin (presumably Colomycin®) in a 22-year old woman with 80% TBSA burns in the U.K. She was initially prescribed a dose of 1MU eight-hourly, but this was increased to 2MU when there was little improvement in her symptoms. Whilst receiving this dose, she developed seizures, which was thought may have been a neurotoxic side-effect of colistin, and the dose was reduced back to 1 MU. The patient’s condition improved and the colistin was stopped. It was restarted when a new septic episode occurred, when the dose was gradually increased from 1MU twelve-hourly to 1.5MU eight-hourly. The patient later died from sepsis-related multi-organ failure.

Blood samples for the patient reported by David and Gill (2008) were analysed by the Antimicrobial Assay Laboratory at Southmead Hospital in Bristol, which is
the same laboratory used for the patient in the current burns study. The pre-dose concentration reported by David and Gill at a dose of 1.5MU was similar to that of the patient receiving the higher dose of 2MU eight-hourly in the current burns study (3.7 vs 3.2mg/L respectively). However, concentrations measured 30 minutes after the end of the infusion were 5.4 vs 9.4mg/L respectively. The target levels quoted by David and Gill (2008) were a pre-dose of 2-6mg/L and post dose 5 – 15mg/L, which were those recommended by the Antimicrobial Reference Laboratory (2007) at Southmead Hospital. These concentrations are lower than the peak of 10 to 15mg/L suggested by the manufacturer and the British National Formulary. They were set following an audit of 220 pre- and post dose serum concentrations. Mean peak concentrations were 9.36 ± 6.12mg/L, and less than 20% were between 10 and 15mg/L (Bowker et al. 2006). The lower peak recommendations were made by the laboratory, despite no dosing or outcome data being available. There were also no data on whether any dose adjustments were made following the reporting of “sub-therapeutic” peak concentrations.

Comparison of the serum concentrations in this study can be made with other studies where the microbiological analysis of serum levels has been used. Data are available from the study by Froman, Gross and Curatola (1970) on which the recommendation of a peak of 10 to 15mg/L appear to be made. However, blood samples were taken after the first dose, at a higher dose, administered over an unknown period of time. Despite this, concentrations appear to be quite similar to those seen in the patient with burns at the 2MU and 2.5MU dose.

Baines and Rifkind (1964) measured serum concentrations using the microbiological assay in patients in the U.S. with infections due to *Pseudomonas* spp. as previously shown in Table 6.4. Despite the higher dose, serum concentrations appeared to be lower than the patient with burns in this study, but in most cases, Baines and Rifkind (1964) took samples on the first or second day of therapy, so the colistin may not have reached steady-state.

The peak concentration measured in the current study was below the mean of 12.3mg/L reported for 23 blood samples from patients with cystic fibrosis
(Conway et al. 1997). However, in the cystic fibrosis patients, eleven peak serum concentrations were below 10mg/L, of which seven were less than 9mg/L. It may be therefore that there are some similarities in colistin pharmacokinetics for both groups of patients.

It is inappropriate to compare the serum concentrations determined microbiologically in this study with studies where analysis has been performed by HPLC. The microbiological method compares the antimicrobial activity of a standard of colistimethate sodium with the activity of the sample. During the time taken for the assay, both the standard and sample are being hydrolysed to colistin.

A study by Bergen et al (2006) concluded that colistimethate sodium has no antibacterial activity against *P. aeruginosa* and is therefore an inactive prodrug of colistin. This was demonstrated by determining bacterial kill over a time period, and frequent assay of both colistin and colistimethate sodium in the solution during this time. Killing was not seen until hydrolysis of the sulphomethate resulted in a concentration of colistin base of 0.5 to 1mg/L (approximately 0.5 to 1 times the MIC for colistin). The reason that previous studies have indicated that the sulphomethate form had antibacterial activity is likely to be due to hydrolysis to colistin during microbiological procedures in the laboratory. This would have wrongly led activity to be attributed to the sulphomethate, when it was in fact due to colistin base. In the study by Bergen et al, 30% of the sulphomethate was hydrolysed to colistin by four hours. Therefore in procedures lasting 24 hours or longer, such as MIC measurement, it is likely that a large proportion of colistin base was present. What is being measured by the microbiological method is therefore likely to be the activity of colistin. What is perhaps therefore surprising is the consistency of data produced by the microbiological method with the plot of concentration versus time appearing as one might expect i.e. a rapid decline corresponding to a distribution phase, followed by a slower decline corresponding to elimination of the drug.
6.5.2. Pharmacokinetic studies of colistin using HPLC analysis

Further work is required to relate the microbiological and HPLC methods, before comparison between studies using the different methods can be made. However a review of pharmacokinetic studies where HPLC analysis has been used that can distinguish between the two forms of colistin is required to aid with the proposal of a dose that should be used in patients with severe burns.

Li et al (2003c) used their HPLC method to study the pharmacokinetics of intravenous colistin sulphate in rats. The method they used was a modification of that previously published (Li et al. 2001a). Pharmacokinetic parameters were similar for colistin, colistin A and colistin B. The same group went on to study the pharmacokinetics of both colistin and its sulphomethate in rats following an intravenous dose of colistimethate sodium (Li et al. 2004). Peak concentrations of colistin were seen in plasma only five to ten minutes after administration, indicating rapid hydrolysis of colistimethate sodium. Both forms of colistin had a distribution phase of about twenty minutes. Colistimethate sodium had a significantly shorter elimination half-life (23.6±3.9min) than colistin (55.7±19.3min). 61.1±14.4% of the dose was recovered in the urine, half of which was in the colistin form.

Li et al (2003a) also found colistimethate sodium had a shorter half-life than colistin in patients with cystic fibrosis (mean 124±52min versus 251±79min respectively. Patients were administered an eight-hourly dose of either 2MU (>50kg bodyweight) or 1MU (<50kg bodyweight). Mean clearance for the sulphomethate form was 2.01±0.46ml/kg/min and the volume of distribution at steady state was 340±95ml/kg. The calculated C\text{max} at steady-state of colistimethate sodium ranged from 3.2 to 13.2mg/L. For colistin the range was 1.2 to 3.1mg/L. At the time this paper was written, it was assumed that colistimethate sodium had antimicrobial activity, and authors quote MICs of 4-16mg/L for it, and 1-4mg/L for colistin. The concentrations measured were therefore thought to be substantially lower than those needed for maximal kill and it was suggested that higher doses may be required to enhance efficacy.
Markou et al. (2008) reported serum concentrations in a prospective study of fourteen critically ill patients receiving intravenous colistimethate sodium (Colistin®) to treat infections caused by multi-drug resistant Gram-negative bacilli. Colistimethate sodium was administered at a dose of 225mg (equivalent to 3MU) every eight or twelve hours, in all but one patient who received 150mg eight-hourly. Samples were collected after at least two days of treatment, and were analysed by HPLC according to the method of Li et al. (2001a), as modified by Ratjen et al. (2006). Only serum concentrations of colistin were determined, as the sulphomethate form was recognised to be inactive. Statistically significant correlations were found between half-life and age (positive correlation), and $C_{\text{max}}$ and $V_d$ (negative correlation). There was no correlation between serum concentrations and creatinine clearance. The pharmacokinetic parameters calculated are shown in Table 6.9. Additionally the $C_{\text{max}}$ to MIC ratio was recorded, which ranged from 1.15 to ≥ 10.28. Treatment was successful in eleven of the fourteen patients. The three patients where treatment failed all had ventilator-associated pneumonia, and all had $C_{\text{max}}$/MIC ratios above the 2 x MIC that Li et al. (2005) have suggested may be a therapeutic target for colistin. The authors suggested that there is no defined target for $C_{\text{max}}$/MIC for colistin, but noted that other concentration-dependent antibiotics have a target ratio of 8 to 10. In this study (Markou et al. 2008) only two patients had a ratio greater than 8, both of whom had a favourable response. However, a favourable response was also seen in the patient with the lowest ratio of 1.15.

A dose of 3MU every eight hours was evaluated in another pharmacokinetic study of colistin (Plachouras et al. 2009) for the treatment of critically ill patients with multi-drug resistant Gram-negative bacteria. Data from eighteen patients with a mean age of 63.6 years were analysed. Two series of blood samples were taken – after the first dose and at steady state – and were analysed by a liquid chromatography-tandem mass spectrometry method after a rapid precipitation step that avoided the significant degradation of colistin and colistimethate sodium. The mean half-life of colistin was twice that reported for the critically ill patients in the study by Markou et al. (2008) (Table 6.9) despite both studies having a similar mean age of patient, and both excluding patients.
with renal impairment. Steady-state peak serum concentrations were similar, but the low peak following the first dose, led the authors to suggest that patients may benefit from receiving a loading dose.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>3MU every 8 or 12 hours</td>
<td>3MU every 8 hours</td>
</tr>
<tr>
<td>Model</td>
<td>NR</td>
<td>1-compartment</td>
</tr>
<tr>
<td>Elimination half-life (h)</td>
<td>7.4 ± 1.7</td>
<td>14.4</td>
</tr>
<tr>
<td>Clearance (L/h)</td>
<td>13.6 ± 5.8</td>
<td>9.09*</td>
</tr>
<tr>
<td>Vd&lt;sub&gt;ss&lt;/sub&gt; (L)</td>
<td>139.9 ± 60.3</td>
<td>189*</td>
</tr>
<tr>
<td>Predicted first dose C&lt;sub&gt;max&lt;/sub&gt; (mg/L)</td>
<td>NR</td>
<td>0.6</td>
</tr>
<tr>
<td>Predicted C&lt;sub&gt;max&lt;/sub&gt; at steady-state (mg/L)</td>
<td>2.93</td>
<td>2.3</td>
</tr>
</tbody>
</table>

* Estimated population parameters. Values are of formed colistin. Vd<sub>ss</sub> is the volume of distribution at steady state.

Concentrations of colistimethate sodium and colistin were measured in the plasma and effluent dialysate in a patient with multi-organ failure receiving continuous venovenous haemodiafiltration (CVVHDF) after twenty days of treatment (Li et al. 2005). The dose the patient received was 150mg once a day initially, but this was reduced to every forty-eight hours after two weeks of colistin therapy. Both colistin and colistimethate sodium were cleared by CVVHDF, and peak concentrations in plasma were 1.84mg/L and 23.3mg/L respectively. As these concentrations were less than twice the MIC for colistin, and less than sixteen times the stated MIC for colistimethate sodium, and trough levels of both fell below the MIC, the authors suggested that a higher dose may have been required. Instead of their dose of 150mg (2.46mg/kg of ideal body weight) every 24 or 48 hours, they suggest 2 to 3mg/kg every twelve hours may be more suitable.
6.5.3. Pharmacodynamic studies of colistin – a literature review from 2002 to 2010

In addition to reports of colistin use in clinical practice, *in vitro* studies have given a little more understanding of the drug itself. Several studies have investigated the pharmacodynamics of the polymyxin antibiotics. A study by Tam *et al* (2005b) indicated that the antibacterial activity of polymyxin B is concentration-dependent, and related to the AUC/MIC ratio. Concentration-dependent killing for colistin has been confirmed in another study (Gunderson *et al*. 2003). Tan *et al* (2007) tested four different regimens of colistin (8-hourly, 12-hourly, 24-hourly at increasing doses and continuous infusion to achieve serum concentrations of 4.5mg/L) against *Acinetobacter baumannii in vitro*. For all four regimens there was extensive bacterial killing within 30 minutes of starting treatment, regrowth from 6 hours, minor or no bacterial killing after the second or subsequent doses, extensive regrowth across the 6 to 24 hour period, and similar normalised area under the bacterial kill-time curves from 0 to 72 hours. Because of the regrowth, the authors suggest that the current dosage of colistimethate sodium may be insufficient to prevent the emergence of resistance.

A similar *in vitro* study (Bergen *et al*. 2008) was conducted to determine the antibacterial effect and emergence of resistance of different dosing regimens (same total daily dose, but at a frequency of eight, twelve and twenty-four hourly) against *P. aeruginosa*. A comparable bacterial kill was seen with all three regimens, but the eight-hourly regimen, which had the highest percentage of time above the MIC, appeared to be the regimen of choice to minimise the emergence of resistance. The authors therefore warn caution to the administration of colistin in extended dosage intervals. This was echoed by Owen *et al* (2007) who undertook an *in vitro* study of colistin against clinical isolates of *A. baumannii*. Whilst rapid concentration-dependent killing was noted, regrowth was seen by three hours. This was substantial at 24 hours, even at concentrations as high as 32 x MIC. Despite these findings, a dose of 6MU every 24 hours for 14 days has been reported to be safe and effective in the treatment of thirteen patients with cystic fibrosis (Rosenvinge, Pressler and Hoiby 2005).
In vitro studies (Owen et al. 2007; Poudyal et al. 2008) have raised concerns as to whether colistin should be used as monotherapy against heteroresistant strains of *A. baumannii* and *K. pneumoniae*. Petrosillo et al (2008) reviewed the microbiological, animal and clinical evidence for the comparative effectiveness of colistin as monotherapy or in combination with another antimicrobial agent. They concluded that there was some evidence of synergy *in vitro* and in animal studies with antibiotics such as rifampicin and beta-lactams. *In vivo*, Conway et al (1997) reported more of the thirty-five patients having a normal C-reactive protein when colistin was used in combination with aztreonam, azlocillin, piperacillin, ceftazidime, imipenem or ciprofloxacin compared with the thirty-six patients receiving monotherapy. Clinical cure or improvement was seen in all patients in both groups. Two other studies have been unable to demonstrate any differences between monotherapy and combination therapy, with either amikacin or a beta-lactam (Linden et al. 2003), or with rifampicin or imipenem (Tascini et al. 2006), although numbers were small.

Since the review by Petrosillo (2008), there has been one further study of colistin combination therapy (Aoki et al. 2009), this time in the mouse model. This suggested that combination therapy may be beneficial, with maximum synergy being seen with rifampicin. They also noted that in their pneumonia model, maximal survival protection was seen with colistin in combination with rifampicin, intranasally, but not intravenously.

6.5.4. Colistin use in patients with burns – a literature review from 2002 to 2010

It was disappointing that only one patient was recruited for this particular study. Therefore it was not possible to achieve the objective of investigating the influence of patient factors on serum concentrations and pharmacokinetic parameters. Before the commencement of the study, several patients had received intravenous colistin for treatment of infections due to multi-resistant *Acinetobacter baumannii* at the study site. However, changes in local resistance patterns prevented the need for colistin, due to a reduction in multi-drug resistant Gram-negative infections. The data collected however are still of
use, as local resistance patterns may once again change. Additionally, the
survey in 2009 (Chapter 2) indicated that there has been an increase in its use
nationally. In the retrospective study from the regional burns centre in
Chelmsford UK (Ganapathy et al. 2010), twenty-nine patients received
intravenous and/or nebulised colistimethate sodium (Colomycin®) for the
treatment of multi-resistant Gram-negative infections. The average total dose
was 69MU (range 1 – 268) but the daily doses were not reported. (Personal
communication with the lead pharmacist for burns at Broomfield revealed that
the standard dose used in adults was 2MU every eight hours.) Most patients
also received concomitant treatment with other antimicrobials. Seventeen
patients received combined intravenous and nebulised colistin, of which seven
survived. Six more patients received only intravenous colistin of which four
survived. Causes of death were not reported. Because of both the expected
high mortality rates in these patients and the many variables, the study did not
determine whether colistin was an effective treatment of MDR Gram-negative
infection in patients with major burns. However there was no significant change
in mean serum creatinine concentrations pre- and post- treatment, indicating
that the drug is unlikely to cause renal impairment in patients with normal
baseline serum creatinine concentrations.

Zhang et al (2009) describe the use of colistin for the treatment of multi-drug
resistant Gram-negative infections in nine patients with major burns in China.
The dose was described as $100 \times 10^4 - 150 \times 10^4$ U/d, with some patients
receiving concomitant administration of nebulised colistin. There was a
bacterial eradication rate of 92.3% in the blood. In the sputum isolation of MDR
Gram-negative bacilli was reduced in seven patients. Gram-negative bacilli
were no longer detected in the urine of one patient being treated for a urinary
tract infection. Colistin was judged to be clinically effective in all but one patient.
The renal function of one patient worsened during treatment but this returned to
normal by one month after treatment. No other adverse effects were noted. The
authors concluded that use of colistin was a good option for treating infections
caused by MDR Gram-negative bacillus in patients with severe burns.
Successful treatment of carbapenem-resistant *K. pneumoniae* in an eighteen year-old with 40% TBSA burns (Benenson et al. 2009) has been reported using colistin in combination with gentamicin. In this case report from Israel, acute bacterial endocarditis developed. Cultures from the blood and burn wound identified a strain of *K. pneumoniae* which was only susceptible to colistin and gentamicin. The patient received colistin 2MU and gentamicin 1.7mg/kg every eight hours and after three weeks, acute renal failure developed. Gentamicin therapy was stopped, but treatment with colistin continued for six weeks, and renal function returned to normal. As both drugs are potentially nephrotoxic, it is possible that the renal failure was due to the combination of the two, rather than specifically to the gentamicin. Follow up cultures were negative and the patient survived.

Goverman et al (2007) undertook a retrospective review of fourteen children in the US aged between two and seventeen years, with total burn surface area ranging from 20 to 93%. Colistimethate sodium was administered for between 3 and 42 days for the treatment of infections caused by either *P. aeruginosa* or *A. baumannii*. All patients had one of these organisms isolated from their blood. Other sites of infection were the lung, wound and urine. Doses were dependent on body weight and creatinine clearance, and ranged from 2.74 to 5.58mg/kg/day. Two also received nebulised colistin. Eleven patients responded quickly, and well, to the colistin and survived. One further patient survived, but required three courses of therapy. Two patients did not respond, and later died. There was a significant rise in the creatinine concentration in two patients. One of these was admitted with septic shock and pneumonia, and died of refractory septic shock 72 hours after initiation of colistin therapy. The second patient had colistin added to amikacin therapy. Two weeks after the discontinuation of both antibiotics, his serum creatinine level had returned to baseline. Creatinine more than doubled towards the end of the course, and concentrations began to drop on the discontinuation of both antibiotics. By two weeks it had returned to baseline. No child developed neurotoxicity attributed to colistin therapy. The authors concluded that the use of colistin in pan-resistant infections appears to be justified.
Rosanova et al (2009) reported the use of colistimethate sodium in 45 children in Argentina with TBSA burns ranging from 9 to 87%. Fourteen patients (31%) were infected by *P. aeruginosa* and twenty patients by *Acinetobacter* spp, with both bacteria found in six patients. Forty patients were infected by multi-drug resistant organisms. The dosage used was 5mg/kg/day up to a maximum of 160mg every six hours. None of the children developed increases in serum creatinine concentrations or neurological complications during treatment with colistin, again indicating that the potential benefits of colistin are likely to outweigh the risk of adverse effects.

6.5.5. Colistin use in patients without burns – a literature review from 2002 to 2010

Studies in non-burn patients include one by Garnacho-Montero et al (2003) which found that colistimethate sodium (Bellon: Rhône-Poulenc Rorer) was effective against carbapenem-resistant *A. baumannii* for the treatment of ventilator-associated pneumonia. Doses were quoted in mg and were similar to those for Coly-mycin M®. Twenty-one patients were treated with colistimethate sodium, where strains of *A. baumannii* were only susceptible to this antibiotic. Fourteen patients were treated with imipenem, against organisms that were not carbapenem-resistant. Differences on the mean APACHE II and SOFA scores between the two groups were not significant. Cure rates and mortality rates were also similar. Colistin did not appear to increase the risk of either renal or neurotoxicity.

Twenty-three patients with serious infections - twenty-two had septic shock and/or renal failure - due to pan-resistant or minimally susceptible *P. aeruginosa*, were treated with colistin (presumably Coly-Mycin®) (Linden et al. 2003). In this group of critically ill patients, a high mortality rate would be expected, and seven patients who had an unfavourable response to colistin died whilst receiving colistin therapy. Two more patients, who had an unfavourable response, died after the completion of therapy. However a favourable clinical response was recorded in fourteen patients. Three of these experienced relapses, but were again successfully treated with colistin. Five patients who had a favourable response to therapy also died, although none of
these deaths were attributed to *P. aeruginosa* infection. Microbiological eradication was recorded in ten cases. One patient developed reversible muscular weakness during therapy. Two patients, who were not receiving renal support at the start of treatment, developed renal failure, one during treatment. This study indicated that colistin may be useful in the treatment of infections caused by multi-resistant *P. aeruginosa*.

Falagas *et al* (2006) retrospectively reviewed patients receiving either colistimethate sodium in combination with meropenem (57 patients) or as monotherapy (14 patients) for the treatment of multi-drug-resistant Gram-negative infections. Mean total daily doses of colistin were 5.5±2.2 MU and 4.6±2.3 MU respectively. There were no significant differences between the groups in patient factors such as age, APACHE II scores and co-morbidities, except that the pathogens isolated in the colistin monotherapy group had a greater incidence of *P. aeruginosa* and infection was more likely to occur in the urinary tract. There were also no significant differences between the groups in their clinical response (resolution or improvement of signs and symptoms by the end of treatment) or the development of signs of nephrotoxicity. Survival in the combination group was significantly lower (63%) compared with the colistin-only group (100%). Even after adjusting for the variables for which significant differences were found, this gave a favourable association for treatment with colistin alone. One explanation for this was the higher incidence of urinary tract infections in the monotherapy group, compared with more severe infections in the combination group.

In a different paper, Falagas *et al* (2005b) also reported no serious toxic effects of colistin (mean total daily dose 4.4±2.1MU) in a retrospective review of fourteen patients when used for at least four weeks. Whilst there were statistically significant rises in serum creatinine during therapy, there were no significant differences in the median serum creatinine concentrations at the beginning and end of therapy. One patient had an increase of more than 50% during treatment. Similar observations were made for blood urea concentrations. One patient developed symptoms of polyneuropathy during treatment, but these improved without the need to stop treatment. Another had
polyneuropathy before treatment commenced, which worsened whilst on colistin, but gradually improved when the drug was discontinued. Three patients had increased levels of hepatic and cholestatic enzymes during administration. These were attributed to one each of acute cholecystitis, severe inflammatory systemic reaction and anti-epileptic medicines.

Falagas et al (2005a) also reported on a prospective study of the adverse effects of colistin (Colomycin®) in twenty-one patients receiving total daily doses ranging from 3 to 9MU per day. On average, there was a non-significant increase in serum creatinine from the start to the end of treatment. Nephrotoxicity was recorded in three patients. This was defined as in increase of more than 50% from the baseline creatinine level to a value of at least 1.3mg/dl, or a requirement to start renal replacement therapy. Two of the patients died for reasons not thought to be related to the decline in renal function. There was a significant correlation with the rise in serum creatinine during therapy and the cumulative dose, but not with the total daily dose. The authors recommended close monitoring of renal function during treatment, and for care to be taken if colistin is prescribed concomitantly with other nephrotoxic drugs.

More recently Gounden et al (2009) retrospectively assessed the safety and efficacy of colistin monotherapy (2MU eight-hourly) compared with tobramycin monotherapy (5 to 6mg/kg daily for patients with normal renal function) for the treatment of multi-drug resistant A. baumannii infections. Colistin (Colimycine®) was prescribed only when the organism was resistant to all other antimicrobials. There were 32 patients in each group, between which there were no significant differences in mean age, mean APACHE score at ITU admission, median baseline creatinine concentration, median length of antimicrobial therapy and sites of A. baumannii infection. Eleven patients (34.4%) receiving colistin died whilst in the ITU compared with seven (21.9%) receiving tobramycin (p>0.05). The differences between the two groups were significant for total in-hospital mortality figures (sixteen (50%) and nine (28.1%) respectively), but the authors judged this as unlikely to be related to the antimicrobial therapy. Both antibiotic groups had similar bacterial eradication rates (50% and 55% respectively) and a
modest increase in creatinine from baseline to the highest recorded creatinine level in the ten days from starting treatment (mean change 42 micromol/L for colistin and 19.6 micromol/L for tobramycin). One patient in the colistin group, who had a high serum creatinine (118 micromol/L) before the start of treatment, required the initiation of haemodialysis after six days. The cause of this may have been the colistin, but equally it could have been due to sepsis. The authors concluded that the data suggested that colistin is not significantly different from tobramycin in both its efficacy and safety, and that colistin is an acceptable choice of therapy for the treatment of infections caused by *A. baumannii*, when resistance is reported to all other antimicrobials.

6.5.6. Colistin dosing options for patients with major burns

In addition to the case study already discussed in Section 6.5.1, David and Gill (2008) reported the continued use of colistin in several patients, including those with burns, at a dose of 2MU eight-hourly provided there was no renal impairment. Serum concentrations were measured after three to five days, and doses adjusted accordingly, taking also into consideration the status of the patient clinically. The authors made reference to the recommendation of a target “peak” plasma level (about 30 minutes post infusion) of 10 to 15mg/L (equivalent to 125 to 200 units/ml) by the manufacturer and in the British National Formulary. They also recognised the uncertainty relating to the extent of hydrolysis of colistimethate sodium, and the fact that HPLC analysis may improve this. They also made reference to the potential effects of altered pharmacokinetics on colistin, and recommended prescribing maximum doses for these patients, possibly up to 3MU every eight hours for life-threatening infections. They concluded that more pharmacokinetic studies are required, particularly in patients with major burns.

It has not been possible to achieve the objective of using pharmacokinetic parameters of colistin to develop dose recommendations for colistimethate sodium in patient with major burns. This is partly because only one patient was recruited to the study, but also because of the lack of evidence of the marker of efficacy of the antibiotic. However considering the critically ill status of a patient with major burns with an infection caused by multi-drug resistant bacteria, it
would seem appropriate that 3MU every eight hours should be the standard adult dose, provided that there is no evidence of renal impairment or low body-weight. In the absence of better evidence, monitoring of serum concentrations should continue, with the goal of a peak of 10 to 15mg/L. These recommendations have been approved at the Queen Victoria Hospital. However, further work is clearly required to determine the best marker of efficacy. A multicentre study is taking place in the US relating pharmacodynamic parameters of both colistin and colistimethate sodium to outcome in 238 patients with pneumonia (Silveira 2007). This is due to be completed in 2012. If successful, this may aid with the application of pharmacokinetic parameters in burns patients to determine the optimal dose.

6.6. Conclusions

This is the first report where pharmacokinetic parameters of colistin have been calculated in a patient with severe burns. The peak and trough serum concentrations were similar to those reported for another patient with burns in the UK. However, it is not possible for comparisons to be made with other pharmacokinetic studies, due to the method used for analysis of samples, and also possible differences between the brands of colistin.

Evidence is weak for the UK recommendation for a target “peak” colistin concentration of 10 to 15mg/L, thirty minutes after the end of infusion. It is likely that if a dose of 3MU eight-hourly had been given to the patient in this study, this target would have been reached, and there is evidence to support this dose in clinical practice. In the absence of a target based on better evidence and given the critically ill status of patients with burns who require treatment of an infection caused by a multi-drug resistant Gram-negative organism, a starting dose of 3MU eight-hourly should be considered for patients without evidence of renal impairment, or low bodyweight. The antimicrobial effectiveness may be enhanced if used concomitantly with other antimicrobials such as rifampicin, although the evidence for this is not conclusive.

The antibacterial activity of colistin is thought to be concentration-dependent. Whilst other antibacterials that exhibit primarily concentration-dependent killing,
such as aminoglycosides, are administered as a single-daily dose, it appears that administration of colistin by this method may be less effective and may increase the risk of development of resistance.

6.7. Recommendations

A dose of colistimethate sodium in the UK of 3MU eight-hourly should be considered in patients with major burns for the treatment of severe infections caused by multi-drug resistant Gram-negative bacteria. A lower dose may be preferred for patients with evidence of renal impairment or low bodyweight. The patient’s renal function, in particular creatinine clearance, should be monitored daily, and colistin serum concentration measurements at steady-state may also be a guide for any dose adjustments. The target should remain as a peak concentration of between 10 and 15mg/L. Care should be taken if colistin is used concomitantly with other potentially nephrotoxic drugs. At present there is insufficient evidence to select other antimicrobials to achieve a synergist effect with colistin.

These recommendations have been made to the multidisciplinary burns team at the Queen Victoria Hospital and the proposals have been agreed for all future treatment of patients with major burns. Adoption of these recommendations may reduce morbidity and mortality of severely burned patients with multi-resistant Gram-negative infections.
Chapter 7 Gentamicin

7.1. Introduction

Gentamicin is an aminoglycoside antibiotic. It is bactericidal and is active against many strains of Gram-positive and Gram-negative pathogens, including *Pseudomonas aeruginosa*. The parenteral preparation is indicated for the treatment of severe infections, including septicaemia, bacteraemia, abscesses, subacute bacterial endocarditis, accidental and operative trauma, and infections of wounds (including burn wounds), the upper and lower respiratory tract and the urinary tract. Additionally it can be used to treat neonatal and gynaecological infections (Hospira 2010; Sanofi-Aventis 2010).

7.1.1. Mode of action and resistance of gentamicin

Aminoglycosides bind to prokaryotic ribosomes, which are highly polar molecules. This enables the passage across the outer-membrane of Gram-negative bacteria. They are then transported across the inner membrane of Gram-negative organisms and also across the cell wall of Gram-positive organisms, where they bind to the 30S sub-unit of ribosomes. This perturbs the proofreading of nascent proteins, and impairs the quality control of the bacterial protein production process, resulting in the insertion of more of aberrant proteins in the cell membrane, so making it less stable. This leads to greater penetration of aminoglycosides and eventually to cell death (Touw, Westerman and Sprij 2009).

There are two main mechanisms of resistance. Firstly there is a reduced uptake and / or reduced accumulation of the aminoglycosides in the bacteria. Secondly bacteria produce enzymes that modify aminoglycosides and so inactivate them (Mingeot-Leclercq, Glupczynski and Tulkens 1999).

7.1.2. Dose and administration of gentamicin

Gentamicin may be administered by intramuscular or intravenous injection, although for the treatment of severe infections, the latter is more common. The
usual recommended total daily dose for patients without renal impairment varies between manufacturers (between 3 and 6 mg/kg/day) and the frequency of administration ranges from once, to four-times, a day.

For once-daily administration, monitoring of serum concentrations is recommended primarily to reduce the risk of toxicity. This is discussed in more detail in Section 7.1.6.

For multiple daily dosing, serum concentration monitoring is also undertaken to increase the likelihood of efficacy (Amdiphar 2009; Hospira 2010; Sanofi-Aventis 2010). For this method of administration, the recommended target gentamicin serum concentrations at the Queen Victoria Hospital are a peak of 5 to 10mg/L (higher end of the range for severe infections, particularly if treating a Gram-negative septicaemia) and a trough concentration of less than 2mg/L (See Appendix 3). Recommendations for peak serum concentrations vary between institutions, for example a recommendation of 10-12 mg/L for Gram-negative sepsis, or 3 to 6mg/L for treatment of susceptible Gram-positive endocarditis (Caldwell 2006). (Patients with Gram-positive endocarditis would not be treated at the Queen Victoria Hospital, a specialist surgical hospital.)

7.1.3. Toxicity

The main adverse effects associated with aminoglycosides are nephrotoxicity and ototoxicity, which occur most commonly in the elderly and in patients with renal failure (BNF 2010). These have been associated with higher trough serum concentrations (Rao, Ahmed and Hagan 2006).

Renal toxicity is due to retention of a small amount (about 5% of the dose) in the S1 and S2 segments of the proximal tubule after glomerular filtration (Mingeot-Leclercq and Tulkens 1999). It is usually reversible and manifests itself by slowly rising serum creatinine concentrations, and hypo-osmolar urinary output (Touw, Westerman and Sprij 2009). Higher peak concentrations are not thought to be more likely to cause it than lower ones. In fact, administration as a single dose once a day in rats was associated with a lower incidence of
toxicity than when the same daily-dose was given in divided doses or as a continuous infusion (Giuliano, Verpooten and De Broe 1986).

Ototoxicity is usually irreversible, due to the destruction of sensory hair cells in the cochlea and the vestibular labyrinth (Touw, Westerman and Sprij 2009) and tends to affect high-frequency hearing before low-frequency hearing (Brummett and Fox 1989). It is thought to be least in partly due to the production of free-radicals (Smith 2000; Leung et al. 2004).

7.1.4. Pharmacokinetics of aminoglycoside antibiotics

In healthy individuals, aminoglycosides have a bioavailability of less than 1% when administered orally (Caldwell 2006). They have very low protein binding (Hermann 2007) and predominantly distribute into body water (as opposed to fat), in particular to extracellular fluids. The volume of distribution of gentamicin is usually taken to be 0.3L/kg (Caldwell 2006). A two compartment model appears to best describe their pharmacokinetics, although in the clinical setting, a one-compartment model is applied for simplicity. The elimination half-life is usually between 3 and 4 hours (McNamara et al. 2001).

Aminoglycosides are mainly excreted by glomerular filtration, but there is also some active secretion (Caldwell 2006).

There have been several reports of the pharmacokinetics of gentamicin and other aminoglycosides in patients with severe burns (see Chapter 1, Section 1.8.1).

7.1.5. Pharmacodynamics of aminoglycoside antibiotics

Aminoglycosides exhibit concentration-dependent killing. Moore et al (1984) analysed four prospective, randomized, and controlled clinical trials of gentamicin, tobramycin, and amikacin in patients (total 89 patients) with Gram-negative bacteraemia, who were treated with aminoglycosides. They found that the $C_{\text{max}}^{19}$ to MIC ratio was the main parameter associated with efficacy; a ratio

\[ C_{\text{max}}^{19} \] was defined as the concentration 1 hour after the start of a 30-minute infusion.
of less than 2 was associated with a response rate of 0.55, which increased to 0.9 when the ratio was between 10 and 12.

Deziel-Evans et al. (1986) also found that a favourable outcome was associated with the C_{max}/MIC ratio (ideally greater than 8) when they retrospectively studied 45 adult patients treated with aminoglycosides for bacterial infections. Additionally in an in vitro pharmacokinetic model of the quinolone, enoxacin, and the aminoglycoside, netilmicin, Blaser et al. (1987) measured for both a 99% reduction of the bacterial counts within 4 hours if the peak concentration was three times the MIC, but that bacterial regrowth occurred within 24 hours unless the C_{max}/MIC ratio exceeded 8.1.

Aminoglycosides are reported to have post-antibiotic effect which gets longer as the peak serum concentration increases (Kapusnik et al. 1988). With a longer post-antibiotic effect, it follows that a drug should be able to be given less frequently to achieve the same therapeutic effect. For aminoglycosides, this would mean that there would be a longer period when serum concentrations were very low compared with more frequent dosing, and hence a reduction in the risk of nephro- and oto-toxicity. Therefore administration of the whole total daily dose as a single dose offers theoretical advantages in terms of both efficacy and toxicity over multiple daily dosing. In vivo and in vitro studies have shown that once-daily administration is at least as effective as multiple daily dose administration, but it is less likely to cause renal toxicity and oto-toxicity (Bennett, Plamp and Gilbert 1979; Sturm 1989; De Vries et al. 1990; Nordstrom et al. 1990; Ter Braak et al. 1990; Beaucaire et al. 1991; Gilbert 1991; Prins et al. 1993; Nicolau et al. 1995).

At the Queen Victoria Hospital it has been the practice to administer gentamicin as a once-daily dose in non-burn patients for many years. The standard dose is 5mg/kg, and doses are adjusted to ensure that the gentamicin serum concentration measured eighteen hours after administration of the dose is 1mg/L or lower (personal experience of the Researcher in the role of clinical pharmacist).
7.1.6. Current practice of aminoglycoside use in patients with burns

The survey in Chapter 2 highlighted the difference in practice of administration of aminoglycosides. A recent review of extended interval dosing (or “once-daily”) gentamicin stated that such administration is not suitable for patients with extensive burns (UKMi 2009). Despite this, all but one site was administering gentamicin by this method. As discussed in Chapter 1 Section 1.8.1, Hoey et al (1997) used pharmacokinetic data from 52 patients receiving gentamicin or tobramycin to calculate pharmacokinetic parameters for simulated single doses of 5 to 7 mg/kg. They concluded that patients with large burns may not be candidates for once-daily administration of aminoglycosides as extrapolated concentrations in some patients fell below 0.1mg/L (their definition of aminoglycoside-free) as early as 7.5 and 8 hours for 5mg/kg and 7mg/kg doses respectively. Whilst the maximal length of the aminoglycoside-free period has not been robustly determined, there is a risk it may be too long in some patients with burns for gentamicin to be efficacious as once-daily administration. Because of this, at the Queen Victoria Hospital aminoglycosides have continued to be administered as a multiple-daily dose. However, administration by multiple-daily dosing reduces the chances of achieving a peak / MIC ratio of 8 to 10, and may increase the risk of toxicity.

In non-burn patents the Hartford nomogram (Nicolau et al. 1995) is one of the methods used to guide dose adjustments for once-daily gentamicin. It is unsuitable in patients who have highly variable or altered aminoglycoside pharmacokinetics, as the dose recommendation of 7mg/kg and dose adjustments assume a volume of distribution of 0.3L/kg. For patients who were over 20% of their ideal body weight20, weight used to calculate the dose was the ideal body-weight plus 40% of the excess weight (0.4 x (actual body-weight – ideal body weight)). The dose was selected in order to achieve a peak/MIC ratio of 10:1. (The MIC of 2mg/L was the median gentamicin MIC for Pseudomonas aeruginosa at their institution. Hence the target peak was 20mg/L.) The dose

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20 Ideal body weight in kg can be calculated from the patient’s height in imperial measurement. IBW is then 2.3 x every inch over 5 foot, plus either 50 for a male, or 45.5 for a female.

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interval was determined to be an aminoglycoside-free period (i.e. less than 0.5mg/L) of at least four hours. In their follow up of 2,184 patients their method appeared to be clinically effective with a low incidence of nephrotoxicity.

An alternative nomogram is the one proposed by Urban and Craig (1997). This is based on a dose of 5mg/kg, and unlike the Hartford Nomogram it has the option of increasing the dose frequency to every twelve hours for patients with very low serum concentrations. The dose of 5mg/kg was selected as this was the maximum daily dose approved by the Food and Drug Administration at that time. Urban and Craig raised concerns at the dose of 7mg/kg, as in the paper by Nicolau et al (1995) the median length of therapy was only three days, and almost all of the patients who experienced nephrotoxicity received treatment for more than this length of time; for patients with Gram-positive endocarditis nephrotoxicity was experienced by 33% of patients and a mean duration of treatment of 6.3 days. However, in the UK extended interval dosing is not recommended for the treatment of infective endocarditis (UKMi 2009). The nomogram proposed by Urban and Craig (1997) is based on an aminoglycoside-free (<1mg/L) period of between 4 and 16 hours. It also incorporates the findings of Blaser et al (1994) who found in their study of 51 patients that with once-daily netilmicin the incidence of nephrotoxicity was 36% when the 8-hour level was greater than 6mg/L (equivalent concentration approximately 5mg/L for gentamicin), but only 9.1% when it was less than this (a significant difference).

Studies of gentamicin in adults with burns found a mean volume of distribution of 0.22 to 0.27L/kg (Sawchuk, Zaske and Cipolle 1977; Zaske, Cipolle and Solem 1978; Polk, Mayhall and Smith 1983; Hoey et al. 1997), but that there was wide inter-patient variation, confirming that the Hartford nomogram should not be applied to this population. However the principles on which the nomogram was based can be used to develop dose adjustment guidelines in patients with severe burns i.e. a target peak concentration of 20mg/L at 1 hour and an aminoglycoside free period of at least four hours.
It is therefore proposed that the dosing schedules for gentamicin and other aminoglycosides, are based on the pharmacodynamic principles on which the Hartford Nomogram (Nicolau et al. 1995) was developed. Despite the concerns expressed by Urban and Craig, this was selected, as the study by Nicolau et al. (1995) assessed the efficacy and tolerability of the Hartford Nomogram in a large number of patients. By applying the mean data from two studies (Zaske et al. 1978; Hoey et al. 1997) of gentamicin in patients with severe burns, the mean dose required to achieve a peak serum concentration (one hour after the start of a 30 minute infusion) of 20mg and a dose interval which includes an aminoglycoside-free period of at least four hours was predicted (Table 7.1). These values appear to be a mean dose of approximately 7mg/kg and a mean dose interval of at least 16 hours.

Both Zaske et al. (1978) and Hoey et al. (1997) report a wide inter-patient variation in the pharmacokinetics of gentamicin in patients with burns. Therefore, data collected as part of routine clinical practice for the administration of multiple-daily dose gentamicin at the Queen Victoria Hospital was analysed to aid with developing a dosing schedule of gentamicin for patients with major burns.

<table>
<thead>
<tr>
<th>Ref</th>
<th>Number of patients</th>
<th>Mean Vd (L/kg)</th>
<th>Mean t½ (h)</th>
<th>Calculated mean Cl (L/hr)</th>
<th>Predicted dose (mg/kg)</th>
<th>Predicted dose interval (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zaske et al (1978)</td>
<td>66</td>
<td>0.22 (0.11-0.52)</td>
<td>2.06 ± 1.85</td>
<td>5.18</td>
<td>6.16</td>
<td>15.97</td>
</tr>
<tr>
<td>Hoey et al (1997)</td>
<td>52</td>
<td>0.27 (0.2 – 0.5)</td>
<td>2.2 (1.0-3.9)</td>
<td>5.95</td>
<td>7.40</td>
<td>16.71</td>
</tr>
</tbody>
</table>

*Table 7.1. Predicted dose and dose interval for extended interval dosing of gentamicin in patients with severe burns*

Mean values for volume of distribution and half-life were used to calculate the clearance, the predicted dose to achieve a peak concentration (at one hour) of 20mg/L and an aminoglycoside-free (<0.5mg/L) period of 4 hours.
7.2. Aims and objectives

The aim of this study is to develop a model for extended interval dosing and monitoring of gentamicin in patients with severe burns. The objectives were:

- To calculate pharmacokinetic parameters such as volume of distribution, clearance and elimination half-life of gentamicin in patients with severe burns from data collected as part of routine clinical practice.
- To use the gentamicin pharmacokinetic parameters calculated to predict the peak (one hour after the start of a 30-minute infusion) serum concentrations and the length of the aminoglycoside-free period that would have been recorded if a dose of 7mg/kg had administered once a day.
- To use the gentamicin pharmacokinetic parameters calculated to predict what dose and dose interval would have been required for each individual patient who received multiple-daily dosing, had administration been as extended interval dosing (Once-daily).
- To propose a model for extended interval dosing and monitoring of gentamicin in patients with severe burns
- To develop an electronic workbook that can be used to aid clinicians with dose adjustments in patients with burns.

7.3. Method

Data from the routine monitoring of patients at the Queen Victoria Hospital who received multiple daily intravenous dosing of gentamicin were recorded as part of a Trust clinical audit. Gentamicin was administered as a bolus dose in line with guidelines developed by the Researcher in the role of clinical pharmacist. These were based on the study by Zaske et al (1991) (See Chapter 1, Table 1.6). The data collected included:

- Patient’s gender
- Patient’s age
- Total body surface area (TBSA) burn
- Burn day when treatment with gentamicin commenced
- Patient’s weight on commencement of treatment with gentamicin
- Serum creatinine on commencement of treatment with gentamicin
- Initial gentamicin bolus dose and frequency
- Peak (1 hour post dose) and trough (immediately before the next dose) gentamicin serum concentrations

From measurement of serum gentamicin concentrations it was possible to calculate pharmacokinetic parameters for each patient. Calculations were based on a one-compartment model and assumed first order kinetics, as is standard practice for interpretation of gentamicin serum concentrations in clinical practice (personal experience of Researcher).

The elimination rate constant, \( k \), was calculated by rearrangement of equation 7.1:

\[
Cp_2 = Cp_1 \times e^{-kt}
\]

**Equation 7.1**

Where \( Cp_2 \) = gentamicin trough concentration in mg/L, \( Cp_1 \) = gentamicin peak concentration in mg/L, \( k \) = the elimination rate constant (hr\(^{-1}\)) and \( t \) = the time between measurement of the peak and trough concentrations (hr).

Rearrangement of Equation 7.1 could then be used to calculate the theoretical serum concentration at time zero, where \( Cp_2 \) was now the concentration of the 1-hour peak concentration, and \( Cp_1 \) was the theoretical concentration at time zero. This then allowed the calculation of the volume of distribution (Equation 7.2).

\[
Vd = \frac{Dose}{Cp_0}
\]

**Equation 7.2**

Where \( Vd \) = volume of distribution (L), \( Cp_0 \) = the theoretical concentration at time zero (mg/L), and dose is expressed in mg.
The total clearance could then be calculated using Equation 7.3

\[ Cl = k \times Vd \]  
Equation 7.3

Where \( Cl \) = total clearance of gentamicin (L/hr), \( k \) = the elimination rate constant (hr\(^{-1}\)) and \( Vd \) = volume of distribution (L)

Elimination half-life could be predicted using Equation 7.4

\[ t_{\frac{1}{2}} = \frac{0.693}{k} \]  
Equation 7.4

Where \( t_{\frac{1}{2}} \) = gentamicin elimination half-life and \( k \) = the elimination rate constant (hr\(^{-1}\))

Applying the pharmacokinetic parameters, and by rearrangement of Equations 7.1 to 7.3, the peak serum concentration, serum concentration at 8 hours and the length of the aminoglycoside-free period\(^{21}\) were predicted for each individual patient if they had been administered a dose of 7mg/kg once a day. Similarly the gentamicin pharmacokinetic parameters calculated were used to predict what dose and dose interval would have been required for each individual patient to have achieved a peak serum concentration of 20mg/L and an aminoglycoside free-period of four hours.

An electronic workbook was then developed, using Excel, based on a one-compartment model, for clinical staff to be able to make dose adjustments in response to serum concentrations measured for future patients receiving extended interval dosing of gentamicin in order to achieve the target peak and dose interval.

7.4. Results

The data from five patients were used for the analysis (Table 7.2). Patients ranged in age from 30 to 45 years. The mean total body surface area (TBSA)

\(^{21}\) The aminoglycoside-free period was the time from when gentamicin serum concentrations were predicted to drop to 0.5mg/L to the time of the next dose.
burn was 46% (range 20 to 80%) and mean weight was 86kg (range 79 to 103kg).

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Sex</th>
<th>Age (years)</th>
<th>TBSA burn (%)</th>
<th>Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>35</td>
<td>80</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>45</td>
<td>20</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>41</td>
<td>45</td>
<td>81</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>39</td>
<td>46</td>
<td>103</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>30</td>
<td>40</td>
<td>79</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>38</td>
<td>46</td>
<td>86</td>
</tr>
<tr>
<td>S.D.</td>
<td></td>
<td>6</td>
<td>22</td>
<td>12</td>
</tr>
</tbody>
</table>

Table 7.2. Demographics of five patients who received intravenous gentamicin by multiple-daily dosing.  
TBSA burn = Total body surface area burn. Weight is the body weight recorded at the time of commencement of treatment of gentamicin. All patients were male.

All patients were commenced on an eight-hourly intravenous gentamicin regimen. The locally recommended dose for the 30 to 60 year age group in severely burned patients was 1.7mg/kg (Appendix 3), rounded off to the nearest practical volume of gentamicin injection to be administered (usually the nearest 20mg/L i.e. 0.5ml). It can be seen that in Table 7.3 that Patients 2 and 5 received a dose slightly higher than this (approximately 2mg/kg). The reason for this may have been that the volume of gentamicin injection to be administered was rounded up to the nearest whole millilitre.

All patients had gentamicin serum trough concentrations of 2mg (the maximum target serum trough concentration) or lower. Three patients had peak serum concentrations within the therapeutic range of 5 to 10mg/L. Patient 2 had peak serum above this (11.8 mg/L) and Patient 5 had a peak serum just below (4.9mg/kg). Doses were adjusted accordingly.
<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Burn day</th>
<th>Initial dose (mg)</th>
<th>Peak serum concentration (1 hour post-dose) (mg/L)</th>
<th>Trough serum concentration (mg/L)</th>
<th>Serum creatinine concentration (micromol/L)</th>
<th>Estimated creatinine clearance (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8</td>
<td>160</td>
<td>8.6</td>
<td>2</td>
<td>124</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>160</td>
<td>11.8</td>
<td>1.2</td>
<td>62</td>
<td>123</td>
</tr>
<tr>
<td>3</td>
<td>22</td>
<td>140</td>
<td>6.8</td>
<td>1.5</td>
<td>55</td>
<td>146</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>170</td>
<td>7.5</td>
<td>1.1</td>
<td>72</td>
<td>144</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>160</td>
<td>4.9</td>
<td>1.2</td>
<td>93</td>
<td>93</td>
</tr>
<tr>
<td>Mean</td>
<td>7</td>
<td>158</td>
<td>7.9</td>
<td>1.4</td>
<td>81</td>
<td>118</td>
</tr>
<tr>
<td>S.D.</td>
<td>9</td>
<td>11</td>
<td>2.6</td>
<td>0.4</td>
<td>28</td>
<td>28</td>
</tr>
</tbody>
</table>

Table 7.3 Patient data at time for the commencement of gentamicin (eight-hourly dosing regimen)

Patients 1 and 2 both received two courses of gentamicin. Data used here is for the first course only. Burn day is the post-burn day on which gentamicin therapy was commenced. Target peak serum concentrations were the higher end of the range of 5 to 10mg/L and a trough of less than 2mg/L. Creatinine clearance was estimated using the Cockcroft and Gault Equation\(^{22}\) (Cockcroft and Gault 1976).

Pharmacokinetic parameters calculated for each patient are shown in Table 7.4. The mean half-life was longer, and both the mean volume of distribution and the mean clearance were smaller than in other pharmacokinetic studies of gentamicin in severely burned patients (Zaske \textit{et al.} 1978; Hoey \textit{et al.} 1997) (Table 7.1). Due to the small number of patients in this study, the values were not compared statistically.

\(^{22}\) The Cockcroft and Gault Equation is \((140 - \text{age in years}) \times \text{bodyweight (kg)} / \text{serum creatinine (mmol/L)}\). This figure is multiplied by 1.23 for males and 1.04 for females.
Table 7.4 Calculated pharmacokinetic parameters for individual patients receiving thrice-daily administration of gentamicin

The mean predicted gentamicin serum concentration for a once-daily dose of 7mg/kg was 31.0 ± 9.5 mg/kg (Table 7.5), with only Patient 5 predicted to have had a peak below 20mg/L. No patients were predicted to have a serum concentration above 5mg/L at eight hours.

Table 7.5 Predicted serum concentrations of gentamicin following a dose of 7mg/kg

The aminoglycoside-free period is the time in the 24 hour dosing interval when gentamicin serum concentrations are below 0.5mg/L.

It can be seen in Table 7.6 that the mean predicted gentamicin dose to achieve a peak serum concentration of 20mg/L for the five patients treated at the Queen
Victoria Hospital was only 5mg/kg. Only one patient would have required a dose higher than 7mg/kg. For all of the patients the dose interval would have been rounded off to 24-hourly.

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Age (y)</th>
<th>TBSA burn (%)</th>
<th>Burn day (number)</th>
<th>Weight (kg)</th>
<th>Serum creatinine (μmol/L)</th>
<th>Dose (mg/kg)</th>
<th>Dose-interval (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>35</td>
<td>80</td>
<td>8</td>
<td>100</td>
<td>124</td>
<td>3.7</td>
<td>22.7</td>
</tr>
<tr>
<td>2</td>
<td>45</td>
<td>20</td>
<td>5</td>
<td>80</td>
<td>62</td>
<td>3.4</td>
<td>16.3</td>
</tr>
<tr>
<td>3</td>
<td>41</td>
<td>45</td>
<td>22</td>
<td>81</td>
<td>55</td>
<td>5.1</td>
<td>22.1</td>
</tr>
<tr>
<td>4</td>
<td>39</td>
<td>46</td>
<td>1</td>
<td>103</td>
<td>72</td>
<td>4.4</td>
<td>18.5</td>
</tr>
<tr>
<td>5</td>
<td>30</td>
<td>40</td>
<td>1</td>
<td>79</td>
<td>93</td>
<td>8.3</td>
<td>23.4</td>
</tr>
<tr>
<td>Mean</td>
<td>38.0</td>
<td>46.2</td>
<td>7.4</td>
<td>88.6</td>
<td>81</td>
<td>5.0</td>
<td>20.6</td>
</tr>
<tr>
<td>S.D.</td>
<td>5.7</td>
<td>21.6</td>
<td>8.7</td>
<td>11.8</td>
<td>28</td>
<td>2.0</td>
<td>3.1</td>
</tr>
</tbody>
</table>

**Table 7.6 Predicted extended interval dose and minimum dose interval of gentamicin required for five patients**

Individual patient data were used to calculate the predicted dose required to achieve a peak concentration (at one hour) of 20mg/L and an aminoglycoside-free (<0.5mg/L) period of 4 hours.

The electronic worksheet to aid with dose adjustment for the extended-interval dosing of gentamicin is shown in Appendix 13.

### 7.5. Discussion

This review indicates that a standard dose of 7mg/kg is a suitable starting dose for extended interval administration of gentamicin in severely burned patients without renal impairment. Based on the mean pharmacokinetic parameters for both published studies (Zaske et al. 1978; Hoey et al. 1997) and the individual data from the five patients at the Queen Victoria Hospital, the initial dose interval could be set at 24 hours. However serum concentrations should be measured at one hour after the start of the 30 minute infusion (“peak level”) and again after a further seven hours. These concentrations will provide the pharmacokinetic data to determine the dose required to achieve a peak
concentration of 20mg/L and guide on an appropriate dose interval to achieve an aminoglycoside-free period of at least four hours. An eight-hour level, if above about 5mg/L may also give an indication of risk of nephrotoxicity. As 7mg/kg is a higher dose than is usually used at the Queen Victoria Hospital (and therefore clinical staff may be concerned at the risk of toxicity) it may also be useful to measure an additional serum concentration eighteen hours after the dose is given. This gives time for the sample to be analysed before another dose is due to be administered, but will also give an indication if serum concentrations are likely to be less than 0.5mg/L by 20 hours (i.e. an aminoglycoside-free period of 4 hours if the dose is administered every 24 hours).

The dose of 7mg/kg applies to patients who do not weigh more than 20% of their ideal body weight. For heavier patients, assuming the patient’s height is known, the bodyweight used to calculate the dose should be the ideal bodyweight plus 40% of the excess bodyweight (Nicolau et al. 1995). For the elderly, e.g. over 70 years, a clinical decision may be made to administer a dose lower than 7mg/kg.

An electronic workbook (Appendix 13) has been developed at the Queen Victoria Hospital to aid pharmacists with dosage guidance in response to the gentamicin serum concentrations measured. However, if dose adjustments are required when a pharmacist is not available e.g. at the weekend, some basic guidance should be to adjust the 1-hour peak serum concentration to achieve a concentration of 20mg/L (dose should be proportional to the serum concentration), and ensure that the 18-hour concentration is 1mg/L or less.

Whilst it can be seen from the data from patients at the Queen Victoria Hospital that for some patients, the peak levels from a dose of 7mg/kg may be much higher than 20mg/L, there is no evidence that such high levels are related to toxicity. Even if this were the case, it is likely that in most cases, only one high dose will be administered before pharmacokinetics can be applied to determine the most appropriate dose. Any concerns relating to the risk of a high peak concentration need to be balanced against the risk of sub-therapeutic dosing in
the treatment of life-threatening infections. In their analysis of four prospective, randomized, and controlled clinical trials of gentamicin, tobramycin, and amikacin in patients (total 89 patients) with Gram-negative bacteraemia, being treated by multiple-daily dose gentamicin Moore et al (1984) found a lower mortality rate when initial therapeutic peak serum concentrations were achieved (> 5mg/L for gentamicin) compared with patients with initial sub-therapeutic concentrations. It is not known whether this applies to the much higher concentrations seen with extended interval administration. However, renal toxicity at least is usually reversible whereas the consequences of treatment failure may not be so.

The exception to the guidelines proposed above would be for patients with renal impairment. At the Queen Victoria Hospital dose guidelines for use of once-daily gentamicin in non-burned patients advise that if the creatinine clearance is less than 50ml/min to wait until serum concentrations are known before administering the next dose, and if creatinine clearance is less than 20ml/min to discuss with the microbiologist. This would seem to be appropriate guidance for patients with severe burns. Where the microbiologist advises that there is no suitable alternative to aminoglycoside therapy for patients with a creatinine clearance of less than 20ml/min, the pharmacist should be contacted for dose guidance.

There are several limitations to this work. Firstly, the assumption has been made that the distribution phase is complete at one hour. Additionally dose and frequency calculations are based on a one-compartment model. McNamara et al (2001) found that the distribution half-life of gentamicin appeared to increase with increasing dose, reaching a mean of 31.1 minutes ± 5.7 with a dose of 7mg/kg. A similar conclusion was reached by Demczar et al (1997) in their study of gentamicin in healthy adults although the distribution half-life for a dose of 7mg/kg was longer (mean 41.6 minutes ± 4.3). Because of the additional extracellular fluid that tends to occur in patients with burns, the distribution phase may be longer still. This indicates that by the time of sampling at 1 hour, the distribution phase may not be complete, and therefore show falsely high \(C_{max}\) estimates. However, in the paper by Moore et al (1984) indicating
maximal efficacy at a Cmax/MIC ratio of 10 to 12, the definition of Cmax was 1-hour after the start of a 30-minute infusion. Whilst it would be possible to measure serum concentrations later than one hour, the theoretical concentration at one-hour would need to be calculated, making it difficult for clinical staff to adjust doses. With a simple target of 20mg/L at the time of measurement, the dose can be adjusted proportionally. For example if the peak concentration was found to be 40mg/L, the dose should be halved. Therefore for practical reasons it seems appropriate to remain with the 1-hour target of 20mg/L. The serum concentrations measured at eight and eighteen hours (provided that gentamicin could still be detected in the latter sample) could be used as the two data points to predict the required dose and frequency in order to determine if they varied notably from the dose and frequency predicted using the one-hour and eight hour concentrations, and hence whether the distribution phase was complete at one-hour.

An assumption is also made that other pharmacokinetic parameters are not dose dependent. In their cross-over study of twelve healthy adults McNamara et al (2001) found a significant difference (p < 0.05) between the mean clearance of a 4.5mg/kg dose (104.1 ml/min/1.73m² ± 12.7) and a 7mg/kg dose (111.1 ml/min/1.73m² ± 11.7). Conversely, Demczar et al (1997) noted a significantly lower clearance (p ≤ 0.001) at the higher dose of 7mg/kg (67.2 ml/min/1.73m² ± 4.2) than with a dose of 2mg/kg (76.6 ml/min/1.73m² ± 6.6). Both of the mean clearance values calculated by Demczar et al (1997) were notably lower than those stated by McNamara et al (2001). Nevertheless, changes in pharmacokinetic parameters at different doses may explain why dose adjustments may not result in concentrations exactly as predicted. However there may be other factors which would also affect this such as changes in renal function or fluid volume.

Despite these limitations it is proposed that a dose of 7mg/kg adjusted to obtain a peak serum concentration of 20mg/L and an aminoglycoside-free period of at least 4 hours may both increase the efficacy and decrease the risk of toxicity in
severely burned patients. Daily measurements of creatinine clearance should be undertaken to detect any deterioration in renal function.

Because of the relatively small number of patients in this study, data should continue to be collected, ideally as part of a multicentre collaboration. This will enable the validation of the proposed guidelines.

7.6. Conclusions and recommendations

An initial dose of 7mg/kg of gentamicin (administered over 30 minutes) is proposed for patients with major burns. For patients who weigh more than 20% of their ideal body weight, dosing should be based on a bodyweight calculated as the ideal body weight plus 40% of the excess weight. For the elderly, e.g. over 70 years, a clinical decision may be made to administer a dose lower than 7mg/kg. The initial dosage interval should be 24 hours.

Serum samples should be measured following the first dose, at the following times after the first infusion:

- one hour (peak)
- eight hours
- eighteen hours

Dose adjustments should then be made to obtain a peak serum concentration (one hour after the start of the infusion) of 20mg/L (range 16 to 25mg/L, but 20 to 25mg/L for severe infections). The dose interval should ensure an aminoglycoside-free period (<0.5mg/L) of at least 4 hours, rounded up to the nearest multiple of 12 hours.

For patients with a creatinine clearance of less than 50ml/min, a second dose should be withheld until the serum gentamicin concentrations are known. Where creatinine clearance is less than 20ml/min, treatment should be discussed with the microbiologist, and where there is no suitable alternative, dose guidance should be sought from the pharmacist.
Medical and nursing staff should be advised to seek the advice of the pharmacist for both the determination of the initial gentamicin dose and the interpretation of serum samples. In the absence of the pharmacist, the dose should be adjusted proportionally to achieve a serum concentration of 20mg/L at 1 hour, and the dose interval increased if the serum concentration at eighteen hours is above 1mg/L.

For the pharmacist an electronic workbook has been developed to aid with more accurate prediction of the required dose and frequency.

The measurement of serum samples should be repeated daily, together with that of creatinine clearance to monitor renal function.

This regimen may increase the likelihood of therapeutic success when treating life-threatening infections in severely burned patients with gentamicin. Additionally it may reduce the risk of patients experiencing both nephrotoxicity and ototoxicity compared with more frequent administration regimens. The workbook developed will aid pharmacists with dose adjustment.

These recommendations have been agreed with the Consultant Microbiologist at the Queen Victoria Hospital and will be proposed to the multidisciplinary burns team for all future treatment of patients with major burns. Adoption of these recommendations may reduce morbidity and mortality in severely burned patients.
Chapter 8. Vancomycin

8.1. Introduction

Vancomycin has been in use for over fifty years (Pea et al. 2009). It belongs to a group of antibiotics, the glycopeptides, which has good activity against Gram-positive bacteria, and is generally reserved for the treatment of infections due to meticillin-resistant *Staphylococcus aureus* (MRSA). Vancomycin is licensed for intravenous administration to treat severe staphylococcal infections which cannot be treated with other effective, but less toxic agents, such as penicillins and cephalosporins. Additionally it can be used as prophylaxis against endocarditis in patients at risk from dental or surgical procedures. It may also be given orally for staphylococcal enterocolitis and pseudomembranous colitis due to *Clostridium difficile* (Wockhardt 2008; Hospira 2009).

8.1.1. Mode of action and resistance

Vancomycin works by binding to the D-ala-D-ala found in the peptidoglycan precursor of the bacterial cell wall. This enables it to inhibit the transpeptidase responsible for the cross-linking of polysaccharide backbone, resulting in inhibition of bacterial cell wall biosynthesis (Boger 2001).

Resistance to vancomycin is caused by operons, a segment of DNA containing adjacent genes including an operator gene, a regulatory gene and structural genes. These encode enzymes which reduce the binding of vancomycin (Courvalin 2006). Glycopeptide-intermediate *Staphylococcus aureus* (GISA) has been reported when vancomycin serum concentrations have been consistently 10mg/L or lower (Rybak 2006).

8.1.2. Dose and administration

The usual recommended dose of vancomycin is 500mg every six hours or 1g every twelve hours, given as an infusion at a rate of no faster than 10mg/minute.
(Wockhardt 2008; Hospira 2009). As it has a narrow therapeutic window, doses are adjusted according the peak and trough serum concentrations. Vancomycin may also be given as a continuous infusion (see Section 8.1.6), although this method of administration is not within the UK license.

**8.1.3. Toxicity**

Potentially the most serious toxic effect of vancomycin is nephrotoxicity, particularly if high doses are used. This is usually suspected if an increase in serum creatinine or a decrease in creatinine clearance is observed. The other well-documented adverse effect is ototoxicity. Additionally if vancomycin is administered too rapidly it may cause flushing if the upper body, known as “red-man syndrome”, or pain and muscle spasm of the chest and back (Wockhardt 2008).

**8.1.4. Pharmacokinetics**

Vancomycin is not orally absorbed. Its binding to protein is reported to range from 10% to 50% (Ackerman et al. 1988; Zokufa et al. 1989; Albrecht et al. 1991; Bailey, Rybak and Kaatz 1991). In patients with normal renal function, it is thought to have a distribution phase of approximately half an hour, and an elimination phase of six to twelve hours. Values for its volume of distribution in non-burned subjects range from 0.4 to 1L/kg (Blouin et al. 1982; Rotschafer, Crossley and Zaske 1982; Matzke, Zhanel and Guay 1986; Golper et al. 1988). Vancomycin is primarily renally cleared (Matzke, Zhanel and Guay 1986).

There have been several reports of the pharmacokinetics of vancomycin in patients with severe burns (see Section 1.8.2).

**8.1.5. Pharmacodynamics**

Vancomycin exhibits time dependent killing (Lowdin, Odenholt and Cars 1998), and as far back as 1961 and it was suggested that vancomycin should be administered to maximise the time that its concentration exceeds the MIC for
the suspected pathogen (Louria, Kaminski and Buchman 1961). However, the post-antibiotic effect of vancomycin appears to be concentration dependent, with concentrations of up to four times the MIC resulting in longer PAEs for both *Staphylococcus aureus* and *Staphylococcus epidermidis* (Lowdin, Odenholt and Cars 1998). Few clinical studies have been able to relate any pharmacodynamic parameters to outcome. An exception to this is Moise-Broder *et al* (2004) who found that a successful outcome was associated with a 24 hour area under the curve (AUC) / minimum inhibitory concentration (MIC) ratio of at least 400.

### 8.1.6. Current dosing regimens

The survey of antimicrobial use (Chapter 2) indicated that some burns centres administer vancomycin as intermittent infusion and others as continuous infusion. An early paper relating to the latter method was published in 1986 (Barois *et al.*) for the treatment of fourteen children with meningeal and / or ventricular infection and 1 case of septicaemia in children. All were cured. Later, a prospective multi-centre randomised study (Wysocki *et al.* 2001) of 160 patients with severe staphylococcal infections showed it to be comparable with intermittent administration in terms both of efficacy and tolerance. Superiority over intermittent infusion has not been demonstrated, although it has been shown to enable faster and more consistent attainment of therapeutic serum concentrations (Wysocki *et al.* 2001; Roberts *et al.* 2008). It has however been argued that continuous infusion is only appropriate for the treatment of staphylococcal infections with MICs of ≤ 1mg/L (Panday and Sturkenboom 2009), as a steady–state concentration of 20mg/L, would result in an AUC of 480mg/L per hour. Therefore if the MIC was 2mg/L or higher, the AUC/MIC ratio would be below 400, potentially resulting in therapeutic failure. This has not been demonstrated clinically. With intermittent administration, it has been recommended that minimum serum concentrations should be in the range of 15 to 20mg/L (ATSIDA 2005), but for continuous infusion target concentrations of up to 25mg/L have been proposed (Vuagnat *et al.* 2004).
Since 2002 the Queen Victoria Hospital has administered vancomycin as continuous infusion for the treatment of infection in critically ill patients with burns. In addition to the theoretical benefits, the change was made because of the difficulties of dose adjustment in response to serum concentrations experienced with intermittent infusion (personal experience of the Researcher in the role of clinical pharmacist). The target steady-state serum concentrations were set as 15 to 25mg/L. Guidelines (Appendix 3) were based on those from the Intensive Care at Guy’s and St Thomas’ Hospital, but adapted to include doses found to be necessary in the study by Conil et al (1994) in 18 severely burned patients. As discussed in Chapter 1 Section 1.8.2, in their eighteen patients with a mean TBSA burn of 40%, Conil et al (1994) found that a higher dose (40mg/kg/day) was required in patients under sixty years, compared with those over 60 years in whom a dose of 35mg/kg/day was sufficient. These doses are both higher than 30mg/kg/day (approximately 2g/day) used in studies in non-burned patients (James et al. 1996; Wysocki et al. 2001). However if the half-life of vancomycin is significantly shortened in patients with burns, as concluded by Garrelts and Peterie (1988), it would be expected that higher doses would be required. In 2006, a retrospective audit was undertaken at the Queen Victoria Hospital because of concerns that the doses being used were resulting in toxic serum concentrations. As a result, dosage guidelines were changed to a standard dose of 2g over 24 hours for patients, with lower doses for patients with evidence of renal impairment. These were developed from the dose of 30mg/kg/day used by Wysocki et al (2001) in a study that was not specific to severely burned patients. However, more recently another dosing schedule has been proposed for patients with severe burns (Dailly et al. 2008) based on creatinine clearance measurements. Additionally, a nomogram has been proposed for patients without burns (Pea et al. 2009).

The aim of this chapter is therefore to use routine patient data to determine the most appropriate dosing guideline for continuous administration of vancomycin in patients with severe burns.
8.2. Method

Data was collected from fifteen patients at the Queen Victoria Hospital with severe burns receiving continuous infusion vancomycin between 2002 and 2009:

- Gender
- Age
- Body-weight
- TBSA burn
- Post-burn day of sampling
- Serum creatinine concentration
- Measured creatinine clearance (where available)
- Dose of vancomycin
- Vancomycin serum concentration at steady-state

As this data was collected as part of routine clinical practice, it was not classed as a clinical trial, and no ethical approval was required.

From this data, vancomycin clearance could be calculated (Equation 8.1).

\[
CL = \frac{IR}{C_{p_{ss}}} \quad \text{Equation 8.1}
\]

\(CL\) = vancomycin clearance (L/hr), IR is infusion rate (mg/hr) and \(C_{p_{ss}}\) is the steady state concentration of vancomycin (mg/L).

The 24-hour dose required to achieve a concentration of 20mg/L (mid-point of therapeutic range) was then predicted according to five methods. From this, the mean of the absolute differences and the mean of the absolute percentage error were applied to indicate which of methods 2 to 5 most closely predicted the serum concentrations calculated by the method most likely to be accurate (method 1).
Method 1: Calculation of vancomycin parameters using measured serum concentrations
By rearranging Equation 8.1, the predicted 24-hour dose to achieve a serum concentration of 20mg/L could be calculated from infusion rates and the resulting serum vancomycin concentrations.

Method 2: Current vancomycin guidelines at the Queen Victoria Hospital
Starting dose was determined as discussed in Section 8.1.6. (Table 8.1)

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Starting daily vancomycin dose (/24 hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal renal function</td>
<td>&gt;50</td>
</tr>
<tr>
<td>Mild impairment</td>
<td>20-50</td>
</tr>
<tr>
<td>Moderate impairment</td>
<td>10-20</td>
</tr>
<tr>
<td>Severe impairment</td>
<td>&lt;10</td>
</tr>
</tbody>
</table>

*Table 8.1: Current vancomycin guidelines for patients with major burns at Queen Victoria Hospital (from 2006)*

Method 3: Previous vancomycin guidelines at the Queen Victoria Hospital
These were based on the method published by Conil *et al* (1994), but adapted for dose-adjustment in renal failure (Table 8.2).
<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Starting daily vancomycin dose (/24 hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal renal function under 60 years &gt; 50</td>
<td>40mg/kg (rounded off to nearest 500mg)</td>
</tr>
<tr>
<td>Normal renal function over 60 years &gt; 50</td>
<td>35mg/kg (rounded off to nearest 500mg)</td>
</tr>
<tr>
<td>Mild impairment 20-50</td>
<td>Reduce dose for normal renal function by 500mg</td>
</tr>
<tr>
<td>Moderate impairment 10-20</td>
<td>Reduce dose for normal renal function by 1g</td>
</tr>
<tr>
<td>Severe impairment &lt; 10</td>
<td>Reduce dose for normal renal function by 1.5g</td>
</tr>
<tr>
<td>Filtration /Diafiltration -</td>
<td>Reduce dose for normal renal function by 1g</td>
</tr>
</tbody>
</table>

*Table 8.2: Previous vancomycin guidelines for patients with major burns at Queen Victoria Hospital (2002 to 2006)*

**Method 4: Vancomycin dosing as proposed by Dailly et al (2008) for patients with burns**

\[
\text{Rate of vancomycin infusion (g/day) = } [0.0205\text{Cl}_{cr} + 3.47] \times [\text{target vancomycin concentration at steady-state (mg/L)}] \times \frac{(24/1000)}{\text{Equation 8.2}}
\]

Where \( \text{Cl}_{cr} \) is creatinine clearance in ml/min
Method 5: Vancomycin dosing as proposed by Pea et al (2009) general patients

\[
[0.029\text{Cl}_{\text{cr}} + 0.94] \times [\text{target vancomycin concentration at steady-state (mg/L)}] \times (24/1000)
\]

Equation 8.3

Where \( \text{Cl}_{\text{cr}} \) is creatinine clearance in ml/min

Where creatinine clearance was not measured, it was calculated by using the formula proposed by Cockcroft and Gault (1976) (Equation 8.4)

\[
\text{Predicted Cr}_{\text{cl}} = \frac{F \times (140 - \text{age}) \times \text{weight (kg)}}{\text{Serum creatinine (μmol/L)}}
\]

Equation 8.4

Where \( F = 1.23 \) for males, and 1.04 for females

\( \text{Cr}_{\text{cl}} \) = creatinine clearance in ml/minute

The following were then calculated:

1. The predicted minimum and maximum doses that could have been given in order to achieve therapeutic serum concentrations (15mg/L to 25mg/L) based on method 1. It was then possible to determine whether the doses predicted each of methods 2 to 5 would have been in range.

2. The predicted serum concentrations using the clearance data from method 1 that would have actually been seen with each of the doses calculated by each of methods 2 to 5.

Methods 2 to 5 were compared statistically with Method 1 in order to determine which one was the most accurate dose predictor. This was done using the Mean Average Difference\(^{23}\) and the Mean Absolute Percentage Error\(^{24}\) using Microsoft Excel\(^{\circledR}\).

\(^{23}\) The Mean Absolute Difference was the average of the difference between the predicted dose to achieve a serum concentration of 20mg/L by the selected method (2 to 5), with those...
8.3. Results

8.3.1. Patient demographics and vancomycin data

Patients ranged in age from 18 to 74 years, and had a mean TBSA burn of 34%. The majority commenced vancomycin therapy relatively early post burn (mean post-burn day 12). Body-weight ranged from 55kg to 104kg (Table 8.3).

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Sex</th>
<th>Age</th>
<th>TBSA burn (%)</th>
<th>Burn day</th>
<th>Weight (kg)</th>
<th>Dose (g/24hr)</th>
<th>Measured serum concentration (mg/L)</th>
<th>Vancomycin clearance (ml/min)</th>
<th>Creatinine Clearance (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>18</td>
<td>25</td>
<td>8</td>
<td>89.7</td>
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<td>155</td>
<td>158</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>21</td>
<td>28</td>
<td>7</td>
<td>88.0</td>
<td>1.5</td>
<td>19.2</td>
<td>54</td>
<td>131</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>23</td>
<td>50</td>
<td>3</td>
<td>81.0</td>
<td>3.5</td>
<td>29.1</td>
<td>84</td>
<td>155</td>
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<td>13.4</td>
<td>104</td>
<td>31</td>
</tr>
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<td>5</td>
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<td>28</td>
<td>28</td>
<td>6</td>
<td>91.0</td>
<td>3.5</td>
<td>17.8</td>
<td>137</td>
<td>177</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>30</td>
<td>60</td>
<td>6</td>
<td>100.0</td>
<td>4.0</td>
<td>25.0</td>
<td>111</td>
<td>128</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>31</td>
<td>20</td>
<td>18</td>
<td>116.0</td>
<td>4.5</td>
<td>13.6</td>
<td>230</td>
<td>229</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>34</td>
<td>20</td>
<td>5</td>
<td>90.0</td>
<td>2.0</td>
<td>13.4</td>
<td>104</td>
<td>183</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>42</td>
<td>35</td>
<td>3</td>
<td>93.0</td>
<td>2.0</td>
<td>23.5</td>
<td>59</td>
<td>178</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>43</td>
<td>70</td>
<td>8</td>
<td>100.0</td>
<td>4.0</td>
<td>28.0</td>
<td>99</td>
<td>104</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>55</td>
<td>32</td>
<td>11</td>
<td>94.0</td>
<td>3.2</td>
<td>30.1</td>
<td>74</td>
<td>106</td>
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<td>12</td>
<td>M</td>
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<td>12</td>
<td>90.0</td>
<td>3.5</td>
<td>38.7</td>
<td>63</td>
<td>47</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>64</td>
<td>17</td>
<td>5</td>
<td>116.0</td>
<td>2.0</td>
<td>20.5</td>
<td>68</td>
<td>102</td>
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<td>14</td>
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<td>2.0</td>
<td>24.5</td>
<td>57</td>
<td>90</td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>74</td>
<td>20</td>
<td>12</td>
<td>91.0</td>
<td>2.5</td>
<td>31.6</td>
<td>55</td>
<td>64</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>42</td>
<td>34</td>
<td>12</td>
<td>92</td>
<td>2.9</td>
<td>22.9</td>
<td>97</td>
<td>126</td>
</tr>
<tr>
<td>S.D.</td>
<td></td>
<td>20</td>
<td>16</td>
<td>10</td>
<td>14</td>
<td>1.0</td>
<td>7.6</td>
<td>48</td>
<td>55</td>
</tr>
</tbody>
</table>

Table 8.3 Patient demographics and vancomycin data

Vancomycin clearance was calculated according to Equation 8.1 using the first serum concentration measured for each patient at steady-state. Creatinine clearance was calculated from plasma creatinine and urine concentration and predicted by Method 1. Therefore, the smaller the MAD, the more accurate a predictor the method was.

24 The mean absolute percentage error (MAPE) was the mean of the absolute value of the difference of the selected method (2 to 5) with the predicted value in method 1, as a percentage of the value predicted by the selected method. Therefore, the smaller the MAPE, the more accurate a predictor the method was.

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diuresis for patient numbers 4 and 10. For the other patients, the formula proposed by Cockcroft and Gault (1976) was applied.

8.3.2. Predicted doses to achieve a serum concentration of 20mg/L

The predicted vancomycin doses from Method 1 required to achieve a serum concentration of 20mg/L ranged from 1.6 to 6.6g/24 hours. As patients 1 to 15 were ordered according to increasing age, an observation was made that dose requirement appeared to peak with patient number 7 who was aged 31 years (Figure 8.1).

For both Methods 2 and 5, which were based on non-burned patients, ten of the predicted doses were below that predicted from measurement of vancomycin concentrations (method 1). For methods 2 and 3, which were based on patients with burns, the majority of predictions were an over-estimate (11 and 9 predictions respectively).

![Figure 8.1 Predicted dose of vancomycin in order to achieve a steady-state serum concentration of 20mg/L.](image)

For each patient, the predicted dose was calculated according to five different methods. Method 1 was likely to be the most accurate as the calculation used actual measurements of vancomycin serum concentrations.
Using the mean average difference it appeared that Methods 4 and 5 were the most accurate for dose calculation. With the mean absolute percentage error, Method 4 appeared to be the best (Table 8.4).

<table>
<thead>
<tr>
<th></th>
<th>Method 2</th>
<th>Method 3</th>
<th>Method 4</th>
<th>Method 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean average difference (MAD)</td>
<td>1.1</td>
<td>1.3</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>S.D.</td>
<td>1.2</td>
<td>0.6</td>
<td>0.7</td>
<td>0.9</td>
</tr>
<tr>
<td>Mean absolute percentage error (MAPE)</td>
<td>55.1</td>
<td>38.3</td>
<td>30.5</td>
<td>46.6</td>
</tr>
</tbody>
</table>

Table 8.4 Comparison of doses calculated by methods 2 to 5 with method 1

No method was a good predictor of the required dose of vancomycin. When the MAD was calculated, the best dose predictors were methods 4 and 5. Using MAPE, the best predictor was method 4.

8.3.3. Therapeutic range

The current method (Method 2) had the highest number of predicted doses within range (Table 8.5), although it also had the most number of doses that would have been sub-therapeutic. Method 3 is predicted to have resulted in the highest number of patients with toxic serum concentrations.
Table 8.5. Number of patients likely to have achieved therapeutic serum concentrations with each predicted dose

Therapeutic serum concentrations were 15 to 25 mg/L. The method predicted to result in the most number of patients (eight) with a therapeutic serum concentration within the therapeutic range was Method 2. However, all of the other seven patients in Method 2 are predicted to have had sub-therapeutic dosing.

As the current method, Method 2, predicted the most number of patients within therapeutic range, the data was analysed further to determine whether there any significant differences in the patients who required doses of 3 g or higher (as predicted by method 1), with those who required less. It can be seen from Table 8.6 that the patients who required the dose increase were significantly younger (p < 0.01) and had significantly higher estimated creatinine clearance values (p = 0.02).
<table>
<thead>
<tr>
<th></th>
<th>Age (years)</th>
<th>Initial % TBSA burn (%FT)</th>
<th>Day post-burn of sampling</th>
<th>Serum creatinine (mmol/L)</th>
<th>Creatinine clearance* (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predicted dose &lt; 3g/24 hours</td>
<td>n</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>51</td>
<td>37</td>
<td>10</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>S.D.</td>
<td>20</td>
<td>16</td>
<td>9</td>
<td>35</td>
</tr>
<tr>
<td>Predicted dose ≥ 3g/24 hours</td>
<td>n</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>28</td>
<td>31</td>
<td>13</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td>S.D.</td>
<td>6</td>
<td>15</td>
<td>13</td>
<td>17</td>
</tr>
<tr>
<td>P</td>
<td>&lt; 0.01</td>
<td>0.47</td>
<td>0.64</td>
<td>0.21</td>
<td>0.02</td>
</tr>
</tbody>
</table>

**Table 8.6 Comparison of factors of between patients who were predicted by Method 1 to require total daily doses of at least 3g with those who were predicted not to.**

* Creatinine clearance was calculated by the Cockcroft and Gault equation (1976).

The serum concentrations that would have been likely using the doses calculated from each of Methods 2 to 5 is shown in Figure 8.2. It can be seen that Method 3 is predicted to have resulted in very high serum concentrations for some patients, whereas the lowest serum concentrations were predicted with Methods 2 and 5.
The actual serum concentrations for doses predicted by Methods 2 to 5 to achieve a serum concentration of 20mg/L were calculated based on the data from method 1. Therapeutic range was 15 to 25mg/L.

8.4. Discussion

This review was indicates that none of the methods assessed were accurate predictors of the dose required of vancomycin to achieve therapeutic vancomycin serum concentrations in severely burned patients. Both of the published dosage guidelines specifically for patients with burns would have resulted in potentially toxic levels in many of the fifteen patients studied, putting them at increased risk of adverse effects, particularly nephrotoxicity. However, the two methods that were not specific to severely burned patients are predicted to have resulted in several patients having sub-therapeutic serum concentrations, putting them at risk of treatment failure. Additionally, as discussed in Section 8.1.1, sub-therapeutic concentrations are also associated with the development of resistant organisms. Method 2, the current method was likely to have resulted in the highest number of patients achieving therapeutic range.
The mean clearance calculated for the fifteen patients was 97ml/min ± 48). This value was similar to the means in other studies in patients with burns (Brater, Bawdon and Anderson 1986; Garrelts and Peteri 1988; Dolton et al. 2010), indicating a representative selection of patients.

Looking at how the individual methods were developed, one would expect Method 4 (Dailly et al. 2008) to be the most accurate, as it was based on data from a relatively large number of patients with burns (70). Using the MAD and MAPE, it would appear that this is the case. However, it was Method 2 that was predicted to have resulted in most number of patients within concentrations within therapeutic range. With Method 4, there were six patients predicted to have had serum concentrations above therapeutic range, and three with sub-therapeutic doses. Using 149 samples from their 70 patients, Dailly et al (2008) found a significant relationship between vancomycin clearance and creatinine clearance (r=0.505, P<0.001). The authors used creatinine clearance values calculated from plasma creatinine and urine concentration and diuresis, rather than estimating it by the Cockcroft and Gault equation. In this review, creatinine clearance was measured for only two of the fifteen patients, leaving thirteen to be estimated by a method that has not shown to be good estimation of true creatinine clearance in severely burned patients (Conil et al. 2007b). Additionally the difficulty in obtaining an accurate measurement of bodyweight in patients with severe burns, as discussed in Section 1.8, may have made the calculated creatinine clearance even less accurate. It may have been preferable to have used ideal bodyweight, but calculation of this requires patient heights, data which were not recorded. In the paper by Conil et al (2007), the Cockcroft and Gault equation appeared to most often underestimate true creatinine clearance. This has also been found to be the case with patients at the Queen Victoria Hospital when both creatinine and creatinine clearance have been measured (unpublished data). Therefore, if measured creatinine clearance values had been used, the doses predicted would have been likely to have been even higher, resulting in more patients with potentially toxic serum concentrations. Dailly et al (2008) recognised limitations of their research, namely that a close relationship between creatinine clearance and vancomycin
clearance did not exist for all of their patients. They suggested that other factors such as the volume of distribution may affect vancomycin elimination. The formula also does not take into account factors such as body-weight which may also be needed for dose calculation. The authors propose that the formula should be evaluated in a future prospective study.

No dose schedule can be recommended with confidence. As the current method (Method 2) would have resulted in the highest number of doses within range, it may be most appropriate to remain with this at present. However, the risk of sub-therapeutic dosing should be considered, particularly if a patient is being treated for a life-threatening infection. It can be seen from Table 8.6 that the patients who were predicted to require doses of at least 3g in 24 hours were significantly younger (P<0.01) and had significantly higher creatinine clearances (P< 0.05) when calculated using the Cockcroft and Gault equation (Cockcroft and Gault 1976).

Whilst limitations of the Cockcroft and Gault equation (1976) are recognised, it would seem appropriate to continue to use Method 2 to determine the initial dose of vancomycin but to consider an initial dose of at least 3g in 24 hours for younger adults with evidence of abnormally high creatinine clearance values. Vancomycin doses should then be adjusted to achieve serum concentrations at steady-state between 15 and 25mg/L.

Multicentre data collection should take place, ensuring accurate measurements of creatinine clearance are recorded, together with other demographic details such as patient height. With a large number of patients it may be possible to evaluate more accurately the methods used for dose calculation.

8.5. Conclusions and recommendations

An accurate method for the prediction of the dose of vancomycin when administered by continuous infusion could not be established. In the absence of these, it would seem appropriate that the standard starting infusion dose remains at 2g/24 hours. Lower doses should be used for patients with evidence
of renal impairment, and doses of at least 3g/24 hours should be considered for young adults with evidence of abnormally high creatinine clearance values.

These recommendations have been agreed with the Consultant Microbiologist at the Queen Victoria Hospital and will be proposed to the multidisciplinary burns team for all future treatment of patients with major burns. Adoption of these recommendations may reduce morbidity and mortality in severely burned patients.
Chapter 9. Conclusions

The work undertaken in this thesis has improved the likelihood of therapeutic success of five antibiotics used to treat infection in adults with major burns, by achieving the following three aims:

- To identify antibiotics used to treat infection in critically ill patients with burns in the UK, where dosage guidelines are conflicting or lacking.
- Where pharmacokinetic data are lacking, to investigate the pharmacokinetic parameters of antibiotics when administered to patients with major burns and to produce dosing guidelines for the use of these antibiotics.
- Where pharmacokinetic parameters are published, to review the appropriateness of current dosage guidance.

The literature search in Chapter 1 identified antibacterial agents where there were no dosage guidelines for patients with major burns. Information on antibiotic use in burns centres in the UK (Chapter 2) was obtained through conducting two surveys, firstly before the study commenced (Allen et al. 2002) and then repeated in 2009 at the end of the study. The first survey aided with the determination of which antibiotics to study. The decision was also influenced by prioritisation of drugs that were used to treat multi-drug resistant organisms, as failure of these drugs could result in no further treatment options with severe consequences for patients. The three antibiotics selected for a pharmacokinetic study were therefore meropenem, linezolid and colistin.

The objectives of the pharmacokinetic study were:

a. To compare the serum concentrations with those required to treat likely infections.

b. To calculate pharmacokinetic parameters such as volume of distribution, clearance and elimination half-life.

c. To compare pharmacokinetic parameters calculated in this study of severely burned patients with other populations.
d. To investigate the influence of patient factors on the serum concentrations and pharmacokinetic parameters.
e. To produce dosage guidelines for the use of these antibiotics in adults with major burns.

With meropenem the recruitment target of twelve patients was achieved. This enabled full analysis of the results. As expected it was found that some patients required larger than the standard dose, and dosage guidelines that were higher than the usual were proposed. Although the recruitment target was not reached for linezolid and colistin, use of the data, combined with further literature review, also enabled the proposal of doses for these antibiotics.

Whilst dosage guidelines were already published for multiple-daily dosing of gentamicin in patients with burns pharmacokinetic, there were no recommendations for its use as extended interval dosing. In Chapter 7, pharmacokinetic data in patients with burns were applied to pharmacodynamic principles to recommend dose and monitoring guidance specifically for these patients.

Dosage guidelines for vancomycin in patients with burns have been published. A review of fifteen patients treated at the Queen Victoria Hospital found that these were not good predictors of dose requirements, but neither were guidelines for patients without burns. A modification of the current local guidance was therefore proposed.

9.1. A model for the dosing of all antibiotic in patients with major burns?

The final objective of the thesis was to ascertain, using the data generated and whether there was a model for the dosing of all antibiotics in burns patients. With meropenem, it was found that age and renal function were likely to be the factors which influence dosage requirements. Because for linezolid and colistin, the recruitment target number was not achieved, this data could not be obtained. However, it has been possible to pool the data from all three studies, together with the data collected for vancomycin to help achieve the final objective. Two patients who received linezolid also received meropenem; one
did not require a dose increase for either antibiotic, and one required a dose increase for both antibiotics. Similarly, the patient who required a dose increase with colistin also had a dose increase with meropenem. The fact that no patient needed a dose increase for one antibiotic, but not for another further suggests that patient factors may influence dose requirements for antibiotics in severely burned patients.

Patient demographics were therefore compared for patients who required a dose increase with those who did not for any patient who received any of meropenem, linezolid, colistin or vancomycin (Table 9.1). Gentamicin data was not included as no patients were predicted to require an extended interval dose higher than that recommended for patient without burns. Patients who received more than one of the antibiotics were included only once.

<table>
<thead>
<tr>
<th></th>
<th>Age (years)</th>
<th>Initial % TBSA burn</th>
<th>Day post-burn of sampling</th>
<th>Serum creatinine (mmol/L)</th>
<th>Creatinine clearance (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No dose increase required</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=</td>
<td>16</td>
<td>16</td>
<td>16</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Mean</td>
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<td>12.9</td>
<td>90.7</td>
<td>128.3</td>
</tr>
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<td>53.0</td>
<td>56.8</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=</td>
<td>14</td>
<td>14</td>
<td>14</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>Mean</td>
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<td>42.5</td>
<td>21.1</td>
<td>53.9</td>
<td>219.3</td>
</tr>
<tr>
<td>S.D.</td>
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<td>19.7</td>
<td>13.3</td>
<td>23.7</td>
<td>62.9</td>
</tr>
<tr>
<td><strong>P value</strong></td>
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<td>0.3472</td>
<td>0.0606</td>
<td>0.0211</td>
<td>0.0004</td>
</tr>
</tbody>
</table>

*Table 9.1 Comparison of factors of between the group of patients who required a dose increase for meropenem¹, linezolid², colistin³ and/or vancomycin⁴ compared with those who did not.*

¹Meropenem > 3g/day, ²linezolid > 1200mg/day, ³colistin > 6MU/day, ⁴Vancomycin ≥3g/day ⁵Where the patient received more than one of the antibiotics, the day of sampling of the first antibiotic was used. ⁶Creatinine clearance was estimated using the Cockcroft and Gault Equation (Cockcroft and Gault 1976). ⁷Serum creatinine concentration not recorded for 1 patient receiving vancomycin.
Patients who required a higher dose were significantly younger than those who did not (P<0.01), but these patients also had significantly lower serum creatinine concentrations (P<0.05) and greater creatinine clearances (P<0.01), as estimated using the Cockcroft and Gault equation (Cockcroft and Gault 1976). As previously discussed, this equation is often an underestimation of true creatinine clearance in patients with major burns (Conil et al. 2007b). Therefore although it appears highly likely that patients with an increased glomerular filtration rate are significantly more likely to require higher doses, further work is required to confirm this.

As discussed in Chapter 1, some studies have found age to be a factor affecting antimicrobial dose requirements in severely burned patients for gentamicin (Zaske et al. 1991) and vancomycin (Conil et al. 1994). Other burns studies have shown glomerular filtration rate to be the main factor determining dose requirements for antibiotic such as vancomycin (Dailly et al. 2008), ceftazidime (using the Cockcroft and Gault equation) (Conil et al. 2007a) and imipenem (Boucher et al. 1990; Dailly et al. 2003a). The only other factor found to affect pharmacokinetic parameters in severely burned patients is a negative correlation between serum total protein concentrations and serum teicoplanin concentrations (Steer et al. 1996). This would be expected as teicoplanin is highly protein bound (Rowland 1990).

Whilst recognising that that the current analysis is only on four antimicrobials, it would appear from this and published literature that age and renal function (as estimated by the Cockcroft and Gault equation) are the most important factors in determining dosage requirements in severely burned patients. Therefore more aggressive dosing in younger adults and / or those with evidence of abnormally high creatinine clearance values should be considered when treating severe infections with antimicrobials where pharmacokinetic data are lacking. However, the pharmacokinetic properties of the drug (e.g. protein-binding) and clinical assessment of the patient should also be considered.
9.2. Use of the study antibiotics in patients with major burns

The use of all five of the antibiotics in this thesis has increased notably in burns centres in the UK since the start of the study (see Chapter 2), confirming the relevance of the pharmacokinetic study to clinical practice. There have also been pharmacokinetic studies published from outside of the UK in patients with burns for meropenem (Lin et al. 2004) and linezolid (Lovering et al. 2009) as discussed in chapters 4 and 5 respectively. Additionally there has been one very recent publication which developed a population pharmacokinetic model in patients with severe burns (Doh et al. 2010). For patients with oedema (as defined by puffy face and pitting oedema in the legs) the mean volume of distribution was 28.1L, whereas for those without oedema this figure was 17.0L. Both of these values are less than the mean of 55L in the current study. However, this may have been at least in part due to the higher mean bodyweight of the patients in the current study (Table 9.2). Despite this, both studies have concluded that clearance and volume of distribution are significantly greater than those reported for non-burn patients. Additionally using local susceptibility data for Pseudomonas aeruginosa Doh et al (2010) predicted that with a dose of 1g eight-hourly the probability of achieving the target of T>MIC of at least 40% was only 58.9%, indicating that higher doses were required in some patients. There were other notable differences between the demographics of the patients in this study and the current study (Table 9.3), which may make it inappropriate to make direct comparisons of the data produced by the two studies. In particular, the study by Doh et al (2010) was undertaken on patients from South Korea, so there may have been race differences in the handling of meropenem. Also, whilst the mean total burn surface area was 49.3%, the range was 3 to 97%. Therefore some of the patients would have sustained burns too small to trigger a systemic hypermetabolic response.
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (Male/Female)</td>
<td>7/5</td>
<td>47/12</td>
</tr>
<tr>
<td>Age (years)</td>
<td>46.0 (27 – 73)</td>
<td>47.3 (19 – 86)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>85.0 (53 – 114)</td>
<td>65.9 (42 – 95)</td>
</tr>
<tr>
<td>TBSA (%)</td>
<td>44.1 (20 – 80)</td>
<td>49.3 (3 – 97)</td>
</tr>
<tr>
<td>ABSI</td>
<td>9.3 (5 – 12)</td>
<td>9.6 (4 – 16)</td>
</tr>
<tr>
<td>Post-burn day</td>
<td>29.8 (5 – 71)</td>
<td>9.2 (4 – 28)</td>
</tr>
<tr>
<td>Creatinine Clearance (ml/min)</td>
<td>200 (54 – 369)$^1$</td>
<td>138 (8.8 – 272)$^2$</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>15 (&lt;10 – 24)</td>
<td>27 (19 – 58)</td>
</tr>
</tbody>
</table>

Table 9.2 Patient demographics for two studies of meropenem in patients with burns

$^1$Creatinine clearance estimated by Cockcroft and Gault. $^2$Creatinine clearance estimated by 24 urine collection (44 patients) or Cockcroft and Gault (15 patients).

The 2009 survey of antibiotic use revealed that all units were using doses of meropenem that this thesis has shown may not have been sufficient in some patients. Also no units, other than the study site, were monitoring serum concentrations, despite the presentation of the data from the first seven patients from this study (Allen et al. 2009). One unit had changed to continuous infusion of meropenem (3g over 24 hours) and was planning to monitor concentrations once funding became available. Similarly with linezolid, no units other than the study site were monitoring serum concentrations, leaving patients at risk of receiving sub-therapeutic doses. A case study of the patient who required a higher dose of both meropenem and linezolid was published in 2010 (Hallam et al. 2010), which may have since had an impact on practice. With colistin, no units were using the higher intravenous dose of 3MU eight hourly, despite the evidence to suggest that this dose may be more efficacious. Serum concentrations were being monitored at least some of the time by all units administering this antibiotic intravenously. The rationale for the selection of patients where units only sometimes monitored concentrations is not known. This survey highlights the need to promote appropriate doses and for the monitoring of serum concentrations for antibiotics where they are not routinely collected.
9.3. Areas for future research

Whilst the aims of this thesis have been achieved, many areas for future research have been highlighted, including:

- More pharmacokinetic studies in patients with major burns of the antibiotics included in this thesis in order to validate the proposals.
- Pharmacokinetic studies of other antimicrobial agents used to treat severe infections in patients with burns, where data is lacking, in order to develop dose recommendations.
- More clinical studies relating patient outcome to pharmacodynamic indices.
- Many areas relating to colistin; pharmacokinetics, pharmacodynamics and assay methods

To ensure sufficient patient numbers, collaborative research is required, involving all of the burns units treating severe injuries in the UK and possibly beyond. In Chapter 2, Section 3.15, the difficulties of recruitment from multicentre studies were discussed. Therefore adequate resources should be identified before the start of any study. Additionally awareness of the potential risk of under-dosing with standard doses of antimicrobials should be promoted through education, which should include publication of the findings of this thesis. Such work will further increase the likelihood of therapeutic success of antimicrobial therapy

9.4. Closing statement

Infection is a major cause of death and illness in patients with major burns (Pruitt 1984; Weber and Tompkins 1993; Law, Blecher and Still 1994; Soltani, Zand and Mirghasemi 1998). The work undertaken in this thesis has added to the body of knowledge of pharmacokinetics of antibiotics in adults with major burns. The research undertaken has led to dose recommendations specifically for these critically ill patients, potentially reducing their risk of morbidity and mortality.
Glossary

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>The process by which the drug goes from the site of administration to the site of measurement (e.g. the blood or plasma). Absorption is usually of most clinical importance when a drug is given orally, as some drugs may be extensively metabolised by the liver before reaching the systemic circulation (first pass metabolism). Drugs that are given intravenously are usually 100% absorbed.</td>
</tr>
<tr>
<td>Acute respiratory distress syndrome (ARDS)</td>
<td>A severe lung disease where inflammation causes impaired gas exchange and therefore hypoxaemia (low oxygen levels). The condition often results in multiple organ failure and death.</td>
</tr>
<tr>
<td>Albumin</td>
<td>A protein that maintains the osmotic pressure of the blood.</td>
</tr>
<tr>
<td>Allograft</td>
<td>The transplantation of organ or tissue from one animal to another, but the same species. In burns, this is usually the transplantation of cadaveric skin.</td>
</tr>
<tr>
<td>Anaemia</td>
<td>A deficiency in the number of red blood cells or their haemoglobin content.</td>
</tr>
<tr>
<td>APACHE II</td>
<td>Acute Physiology and Chronic Health Evaluation II, a measure of the severity of illness in intensive care patients.</td>
</tr>
<tr>
<td>APTT (Activated partial thromboplastin time) ratio</td>
<td>A measure of the blood’s ability to clot. In healthy individuals not receiving medicines that affect clotting this value would be close to 1.0.</td>
</tr>
<tr>
<td>Areflexia</td>
<td>Having no reflexes</td>
</tr>
<tr>
<td>Arteriole</td>
<td>A small branch of an artery that leads to the capillary</td>
</tr>
<tr>
<td>AUC</td>
<td>Area under the curve. This usually refers to the area under the curve of a plot of concentration versus time.</td>
</tr>
<tr>
<td>Ataxia</td>
<td>Lack of coordination of voluntary muscle movements</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
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<td>-------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Autograft</td>
<td>Tissue or bone transplanted from one site on an individual’s body to another site</td>
</tr>
<tr>
<td>Bacterial translocation</td>
<td>The movement of bacteria across the intestinal membrane to sites such as the lymphatics, lungs, liver, spleen, kidney and blood</td>
</tr>
<tr>
<td>Bioavailability (F)</td>
<td>The percentage or fraction of the administered dose which reaches the systemic circulation</td>
</tr>
<tr>
<td>Breakpoint</td>
<td>A concentration used in the interpretation of results of susceptibility testing to define isolates as susceptible, intermediate or resistant. For example, a (susceptibility) breakpoint of 4mg/L would mean that organisms susceptible to the antibiotics would have an MIC no higher that 4mg/L</td>
</tr>
<tr>
<td>Capillary</td>
<td>The smallest of the blood vessels, which are only one cell thick. This is where water, oxygen, carbon dioxide and other substances are exchanged between the blood and the tissues</td>
</tr>
<tr>
<td>C.diff</td>
<td><em>Clostridium difficile</em> – a Gram-positive bacteria that causes diarrhoea, usually when antibiotics have affected the balance of the normal gut flora</td>
</tr>
<tr>
<td>Central venous catheter</td>
<td>A catheter placed into a large vein. It has many uses including the administration of medicines, taking blood for testing and measuring the central venous pressure</td>
</tr>
<tr>
<td>Central venous pressure</td>
<td>An indication of the amount of blood returning to the heart and the ability of the heart to pump the blood around the body</td>
</tr>
<tr>
<td>cfu/ml</td>
<td>cfu stands for &quot;colony forming units&quot;. It is used to determine the number of viable bacterial cells in a sample per mL, so indicating the magnitude of the infection in humans and animals</td>
</tr>
<tr>
<td>Clearance (Cl)</td>
<td>The ability of the body or its organs of elimination</td>
</tr>
</tbody>
</table>
(usually the liver or kidneys) to remove the drug from the blood or plasma. Clearance is expressed as a volume per unit of time e.g. L/hr or ml/min and is the theoretical volume of blood that is completely cleared of drug over a given period of time

**Colloidal solution**
An intravenous solution containing finely dispersed particles. These are used in therapy because the particles may be too large to pass through capillaries, thus maintaining an osmotic (oncotic) pressure, and helping fluid to remain in the intravascular compartment

**Concentration-dependent killing**
Where the effectiveness of an antimicrobial increases as its concentration increases at the site of infection. Prolonging the length of time that the drug is at the site of infection will not improve efficacy

**Contracture**
Tightening of the skin. This may result in deformity across joints which will require surgery to release the skin and skin grafting

**CPR (Cardiopulmonary resuscitation)**
Emergency procedure following cardiac or respiratory arrest

**CRP (C-reactive protein)**
A non-specific marker of inflammation and infection

**Crystalloid solution**
An intravenous fluid of water and glucose and / or electrolytes that are dissolved in the solution.

**Cytokine**
A number of substances that are secreted by specific cells of the immune system which carry signals locally between cells.

**Debride**
Removal of dead, contaminated or adherent tissue or foreign material. For burns this is usually a surgical procedure

**Diplopia**
Double vision
<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disseminated intravascular coagulation (DIC)</td>
<td>A clotting disorder than can result in fatal haemorrhage</td>
</tr>
<tr>
<td>Distribution</td>
<td>The process of reversible transfer of drug to and from the site of measurement</td>
</tr>
<tr>
<td>Dyscrasias (blood)</td>
<td>When the constituents of the blood are abnormal or are present in abnormal quantities</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>Difficulty with swallowing</td>
</tr>
<tr>
<td>Dysphonia</td>
<td>Difficulty with making sounds by the voice</td>
</tr>
<tr>
<td>Elimination</td>
<td>Removal of the active drug from the body by metabolism and / or excretion</td>
</tr>
<tr>
<td>Elimination Rate Constant (k)</td>
<td>Used to calculate how drug plasma levels will change with time when the drug is eliminated by first order pharmacokinetics i.e. logarithmically. With first order kinetics, the amount of drug that is eliminated is higher when serum concentrations are higher, but the fraction of the total amount of drug in the body that is removed at any instant in time is constant, and is independent of dose. This fraction is expressed by the elimination rate constant, and is inversely proportional to the elimination half-life</td>
</tr>
<tr>
<td>Empirical therapy</td>
<td>Treatment of infection in response to clinical symptoms, where the causative organism has not yet been isolated</td>
</tr>
<tr>
<td>Endotoxin</td>
<td>A toxin that is confined inside the microorganisms and is released only when the microorganisms are broken down or die</td>
</tr>
<tr>
<td>Endotracheal intubation</td>
<td>The process of inserting a soft plastic cuffed or uncuffed tube through the mouth or nose, past the epiglottis into the bronchus</td>
</tr>
<tr>
<td>Enteral feeding</td>
<td>Administration of liquid food through a tube into the</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
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</tr>
<tr>
<td>Erythema</td>
<td>Redness of the skin</td>
</tr>
<tr>
<td>Eschar</td>
<td>A slough or piece of dead tissue (scab) that is cast off from the surface of the skin, particularly after a burn injury</td>
</tr>
<tr>
<td>Escharotomy</td>
<td>An incision through the eschar to expose the fatty tissue below. This is usually done to relieve the pressure from oedema due to a circumferential chest burn, so improving ventilation</td>
</tr>
<tr>
<td>Excretion</td>
<td>Physical removal of a drug or its metabolite from the body</td>
</tr>
<tr>
<td>Exudate</td>
<td>A fluid rich in protein and cells that oozes out of blood vessels due to inflammation. In the case of burns, exudate usually refers to the fluid lost through the burn wound</td>
</tr>
<tr>
<td>Facultative anaerobes</td>
<td>An organism which can grow without oxygen, but if present can utilise it.</td>
</tr>
<tr>
<td>FiO2</td>
<td><em>Fraction of inspired oxygen</em></td>
</tr>
<tr>
<td>Formulary</td>
<td>A recommended list of medicines</td>
</tr>
<tr>
<td>Full-thickness skin graft</td>
<td>Full layer of skin (epidermis and all of the dermis) used for skin grafting</td>
</tr>
<tr>
<td>GCS</td>
<td>Glasgow coma scale – a scale to measure the level of consciousness. Points for different criteria are added up. The minimum score of 3 indicates deep unconsciousness, and the maximum of 15 indicates full consciousness</td>
</tr>
<tr>
<td>Glycopeptide</td>
<td>Antimicrobials such as vancomycin and teicoplanin, generally reserved for the treatment of multi-resistant Gram-positive infections, particularly MRSA</td>
</tr>
<tr>
<td>Gram staining</td>
<td>A method to classify bacterial species into two groups; Gram-positive and Gram-negative. These</td>
</tr>
</tbody>
</table>
groups differ in the structure of their cell walls, which help determine the choice of antibiotic

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>GRE</td>
<td>Glycopeptide-resistant <em>Enterococcus</em></td>
</tr>
<tr>
<td>Half-life (t½)</td>
<td>Usually refers to the elimination half-life and is inversely proportional to the elimination rate constant, and is the time required for the concentration of a drug to decrease by one-half</td>
</tr>
<tr>
<td>Hartmann’s solution</td>
<td>A crystalloid intravenous solution that is isotonic with blood</td>
</tr>
<tr>
<td>Haematocrit</td>
<td>The proportion of blood volume that is red blood cells. In the initial treatment of burns it helps to give an indication of intravenous fluid volume requirements. It is normally about 48% for men and 38% for women</td>
</tr>
<tr>
<td>Haematological</td>
<td>Relating to the blood and blood-producing organs</td>
</tr>
<tr>
<td>Haematoma</td>
<td>Extravasation of blood outside of the blood vessels.</td>
</tr>
<tr>
<td>Haemodyalysis</td>
<td>A method for removing metabolic waste products, toxic substances and/or free water from the blood usually when the kidneys are in failure</td>
</tr>
<tr>
<td>High extraction</td>
<td>Where a large fraction of drug is eliminated from the body during a single pass through an organ such as the liver.</td>
</tr>
<tr>
<td>HPLC</td>
<td>High performance liquid chromatography. A method using chromatography to separate, identify, and quantify compounds.</td>
</tr>
<tr>
<td>Humoral Immune Response</td>
<td>The aspect of immunity that is mediated by secreted antibodies.</td>
</tr>
<tr>
<td>Hypertrophic scar</td>
<td>A raised and red scar, similar to a keloid scar, but differs as it stays within the boundaries of the injury site</td>
</tr>
<tr>
<td>Hypoxaemia</td>
<td>A low concentration of oxygen in arterial blood</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Inotrope</td>
<td>A drug that increases myocardial contractility, and is used to support cardiac function when blood pressure is low.</td>
</tr>
<tr>
<td>(Clinically) Intermediate breakpoint</td>
<td>A level of antimicrobial susceptibility associated with an uncertain therapeutic effect. It implies that an infection due to the isolate may be appropriately treated in body sites where the drugs are concentrated or if higher dose than usual is used.</td>
</tr>
<tr>
<td>Interstitium</td>
<td>The space between the vascular and cellular compartments</td>
</tr>
<tr>
<td>Intravascular space</td>
<td>Within the blood vessels i.e. space occupied by the blood</td>
</tr>
<tr>
<td>Intubation</td>
<td>Generally refers to tracheal intubation, where a flexible plastic tube is inserted into the trachea to protect the patient's airway and provide a means of mechanical ventilation.</td>
</tr>
<tr>
<td>Isotonic</td>
<td>Having the same osmotic pressure</td>
</tr>
<tr>
<td>Keloid scar</td>
<td>A type of scar that continues to grow beyond what is needed at the site of a healed injury. This type of scar is caused by too much collagen forming while the skin is being repaired.</td>
</tr>
<tr>
<td>Kolff twin coil artificial kidney</td>
<td>A form of haemodialysis developed in the 1950s</td>
</tr>
<tr>
<td>Low extraction</td>
<td>Where a small fraction of drug is eliminated from the body during a single pass through an organ such as the liver</td>
</tr>
<tr>
<td>Lund and Browder Chart</td>
<td>Chart used to indicate the extent, location and depth of burns</td>
</tr>
<tr>
<td>Macrophage</td>
<td>A type of white blood cell which phagocytes (engulfs and then digests) cellular debris and pathogens either as stationary or as mobile cells, and</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>Stimulates lymphocytes and other immune cells to respond to the pathogen</td>
</tr>
<tr>
<td>“Major” burn</td>
<td>Generally accepted to be over 15% TBSA burn in adults or over 10% in children. Also referred to as a severe burn</td>
</tr>
<tr>
<td>Modified controlled effective regrowth time (mCERT)</td>
<td>A measure of bactericidal activity and post-antibiotic effect</td>
</tr>
<tr>
<td>Meshed graft</td>
<td>Where the tiny cuts are made into the donor site so that it appears like lattice work. This enables a larger area to be grafted. The extent of the cutting is described as a ratio; a 2:1 ratio will cover a smaller area than a 4:1 ratio.</td>
</tr>
<tr>
<td>Metabolism</td>
<td>The process of converting a drug to another molecule. Metabolites are often inactive, but may have a pharmacological effect. Some drugs, known as prodrugs, need to be metabolised to another form to become active.</td>
</tr>
<tr>
<td>Midazolam</td>
<td>A sedative agent</td>
</tr>
<tr>
<td>Minimum bactericidal concentration (MBC)</td>
<td>The MBC is the lowest concentration of an antibiotic that kills 99.9% of the original inoculum in a given time</td>
</tr>
<tr>
<td>Minimum inhibitory concentration (MIC)</td>
<td>The MIC is the lowest concentration of the antibiotic that results in inhibition of visible growth (i.e. colonies on a plate or turbidity in broth culture) under standard conditions.</td>
</tr>
<tr>
<td>Monte Carlo Simulation</td>
<td>A method to evaluate the probability of experimental dosage regimens in attaining pre-specified pharmacodynamic targets against specific pathogens</td>
</tr>
<tr>
<td>MRSA</td>
<td>Meticillin-resistant <em>Staphylococcus aureus</em> (formerly known as Methicillin-resistant <em>Staphylococcus aureus</em>)</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSSA</td>
<td>Meticillin-sensitive <em>Staphylococcus aureus</em> (Formerly known as Methicillin-sensitive <em>Staphylococcus aureus</em>)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>Low concentrations of neutrophils in the blood</td>
</tr>
<tr>
<td>Neutrophil</td>
<td>A type of white blood cell</td>
</tr>
<tr>
<td>Nephrotoxicity</td>
<td>Toxicity to the kidney</td>
</tr>
<tr>
<td>Noradrenaline</td>
<td>An inotropic agent, i.e increases cardiac contractility</td>
</tr>
<tr>
<td>Normal saline</td>
<td>A sterile solution of sodium chloride which is isotonic with blood</td>
</tr>
<tr>
<td>Oliguria</td>
<td>Low urine output</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>Cavity formed by the pharynx at the back of the mouth</td>
</tr>
<tr>
<td>Oxygen saturation</td>
<td>The percentage of haemoglobin binding sites in the bloodstream occupied by oxygen. A normal value in a healthy subject is usually at least 98%, but in patients a figure of at least 90% is usually the target</td>
</tr>
<tr>
<td>Paraesthesia</td>
<td>Abnormal skin sensations e.g. tingling, pricking, numbness, itching or burns due to peripheral nerve damage</td>
</tr>
<tr>
<td>Paralytic ileus</td>
<td>Obstruction of the intestine due to paralysis of the intestinal muscles</td>
</tr>
<tr>
<td>Parenteral</td>
<td>Not administered via the gut. In practice, this usually means an injection</td>
</tr>
<tr>
<td>Parkland Formula</td>
<td>A formula to calculate the fluid requirements of a patient with a major burn (&gt;15% TBSA) in the first 24 hours post-injury</td>
</tr>
<tr>
<td>PEEP</td>
<td>Positive End-Expiratory Pressure</td>
</tr>
<tr>
<td>Pharmacodynamics (PD)</td>
<td>The relationship between serum concentrations and the pharmacological and toxicological effects of drugs. See also pharmacokinetics.</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Pharmacokinetics (PK)</td>
<td>Quantification of the processes that happen to drugs as they move through the body (absorption, distribution, metabolism and elimination). In simple terms, it is the study of what the body does to a drug, as opposed to pharmacodynamics, which is the study of what the drug does to the body.</td>
</tr>
<tr>
<td>Pleural cavity</td>
<td>The body cavity that surrounds the lungs.</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>Air in the pleural cavity which can lead to a collapsed lung.</td>
</tr>
<tr>
<td>Positive fluid balance</td>
<td>Where the fluid intake is greater than the fluid loss.</td>
</tr>
<tr>
<td>Post antibiotic effect (PAE)</td>
<td>The time it takes for an organism to recover from the effects of exposure to an antimicrobial i.e. the time where there continues to be an antimicrobial effect, despite the site being free of the antibiotic.</td>
</tr>
<tr>
<td>Positive end-expiratory pressure (PEEP)</td>
<td>Continuous pressure to the lower airways at the end of the breathing cycle. This prevents the alveoli from collapsing.</td>
</tr>
<tr>
<td>Pre-albumin</td>
<td>Serum and cerebrospinal fluid carrier of thyroxine, also called transthyretin (TTR).</td>
</tr>
<tr>
<td>Prodrug</td>
<td>A substance that needs to be metabolised to another form to become active.</td>
</tr>
<tr>
<td>Ptosis</td>
<td>Drooping of upper eye lid due to muscle paralysis and weakness.</td>
</tr>
<tr>
<td>Pyrexial</td>
<td>High body temperature.</td>
</tr>
<tr>
<td>(Clinically) resistant breakpoint</td>
<td>Level of antimicrobial sensitivity which results in a high likelihood of therapeutic failure.</td>
</tr>
<tr>
<td>Sebaceous gland</td>
<td>Small oil-producing gland in the skin, usually connected to a hair follicle by a duct into which it releases sebum, which makes up the slightly greasy film on the skin that helps keep it flexible and prevents too much water loss or absorption.</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>“Sectioned”</td>
<td>Detained under the Mental Health Act</td>
</tr>
<tr>
<td>Sepsis</td>
<td>SIRS with the presence of infection</td>
</tr>
<tr>
<td>Septicaemia</td>
<td>Systemic illness caused by microbes in the blood</td>
</tr>
<tr>
<td>“Severe” burn</td>
<td>Generally accepted to be over 15% TBSA burn in adults or over 10% in children. Also referred to as a major burn</td>
</tr>
<tr>
<td>Shock</td>
<td>The inability of the circulatory system to meet the needs of tissues for oxygen and nutrients and the removal of their metabolites</td>
</tr>
<tr>
<td>Slough</td>
<td>Dead tissue in a wound.</td>
</tr>
<tr>
<td>Short Synacthen® test</td>
<td>A test used to detect adrenal insufficiency, which may result in low blood pressure, and affect electrolyte balance</td>
</tr>
<tr>
<td>SIRS (systemic inflammatory response syndrome)</td>
<td>See section 1.4.1</td>
</tr>
<tr>
<td>SOFA</td>
<td>Sequential Organ Failure Assessment, a scoring system for organ failure and multiple-organ dysfunction syndrome</td>
</tr>
<tr>
<td>Split skin graft (SSG)</td>
<td>Where a thin layer of skin (epidermis and variable amounts of dermis) is used for grafting. This is usually meshed.</td>
</tr>
<tr>
<td>Steady-state</td>
<td>When the rate of input is equal to the rate of elimination. In practical terms this is achieved after four to five half-lives.</td>
</tr>
<tr>
<td>(Clinically) Susceptible breakpoint</td>
<td>Level of susceptibility associated with a high likelihood of clinical success</td>
</tr>
<tr>
<td>T &gt; MIC</td>
<td>Percentage of the dose interval where concentrations exceed the MIC</td>
</tr>
<tr>
<td>T cells (T lymphocytes)</td>
<td>A group of white blood cells known as lymphocytes,</td>
</tr>
</tbody>
</table>
which play a central role in cell-mediated immunity.

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tachycardic</td>
<td>Fast heart rate</td>
</tr>
<tr>
<td>Tachypnoeic</td>
<td>Fast breathing rate</td>
</tr>
<tr>
<td>Time-dependent killing</td>
<td>Where the effectiveness of an antimicrobial increases as the time of exposure of the drug at the site of infection increases. There is usually a minimum concentration of the drug required, but increasing the concentration above this will not increase efficacy.</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Low numbers of platelets</td>
</tr>
<tr>
<td>Thromboembolic events</td>
<td>Clotting events that cause a blockage of blood vessels, such as deep vein thrombosis (DVT) or pulmonary embolism (PE)</td>
</tr>
<tr>
<td>Total Body Surface Area (TBSA)</td>
<td>The percentage surface area of the body that has been burnt, excluding superficial burns</td>
</tr>
<tr>
<td>Toxic shock syndrome</td>
<td>Syndrome caused by toxins released by bacteria which can be fatal. Children with burns appear to be at a higher risk of this compared with the general population. Symptoms include high fever, vomiting, hypotension, diarrhoea and rash.</td>
</tr>
<tr>
<td>Transferrin</td>
<td>A plasma protein that carries iron</td>
</tr>
<tr>
<td>Ventilation</td>
<td>Refers to mechanical ventilation, where a machine moves air into and out of the lungs.</td>
</tr>
<tr>
<td>Venovenous hemodialfiltration</td>
<td>A process similar to haemodialysis where patients blood flows out of a vein through a tube, passing through a filter where waste products and water are removed. Replacement fluid is then added and the blood is returned back to the body.</td>
</tr>
<tr>
<td>Venule</td>
<td>A little vein that connects capillaries and veins</td>
</tr>
</tbody>
</table>
| Volume of Distribution (Vd) | The theoretical volume of a compartment required to account for the total amount of the drug if it were present throughout the body at the same
concentration (also known as the apparent volume of distribution). Therefore a drug that is largely taken up into the tissues or fluids outside of the plasma compartment will have a much greater volume of distribution than one that remains mainly in the plasma compartment. Volume of distribution is usually expressed in Litres or Litres/kg of bodyweight.

Y-site compatibility

The compatibility of two or more solutions when infused through the same line.
References

ABPI (2001). Medicines Compendium, Datapharm Communications Ltd.


cephalosporins. *Diagnostic Microbiology and Infectious Disease* 22(1-2): 89-96.


Panday, P. N. and Sturkenboom, M. (2009). Continuous infusion of vancomycin less effective and safe than intermittent infusion, based on


Appendices

Appendix 1. Questionnaire for use of medicines in UK burns units 2001

Do you work in burns? Ever wondered what other burns units in Great Britain are prescribing? Now is your chance to find out.

Complete this questionnaire and we will send you a booklet containing information on drug use in other units.

This questionnaire has been prepared by pharmacists for burns centres in the London area. The main aims are to:

- print a booklet containing the information gathered. This will only be sent to other units that have completed the questionnaire. We have asked you for a contact name, so that other hospitals know whom to contact if they have a query about drug use in your burns unit.
- publish the main findings. This will not contain any names, or identify what individual hospitals are using.

The questionnaire is quite long, but we feel this is necessary. Please take the time to complete it. We have tried to save time by including tick boxes etc, but also please write comments if you have any.

The Questionnaire is divided into six sections:

Drugs in the Resuscitation Period
Intensive Care
Infections and antibiotics
Drugs in all burns
Feeds
Other drugs

In many places throughout the questionnaire, you are asked to insert a number to indicate level of usage of drugs. This should be as follows:

Insert 1 if always or often
2 if sometimes or occasionally
3 if never
Space is left for you to write down any other drugs you have used. Please write the appropriate number to indicate how often you use it.

If you have any queries, please contact Jane Allen, Principal Clinical Pharmacist at the Queen Victoria Hospital in East Grinstead, on 01342 410210 bleep 214 or e-mail jane.allen@qvh-tr.sthames.nhs.uk.

*Please return this questionnaire in the envelope provided, as early in January as possible.*

**Drugs in the Resuscitation Period**

**Fluids**

Please tick which fluid regimen you use for resuscitation in major burns.

- (iii) Resuscitation formula / fluid
  - Adults
    - Parkland (Hartmann’s 4ml/kg/%TBSA over 24 hours)
    - Muir and Barclay – which colloid?
  - Other (Please state fluid used and regimen)

- (iii) Children
  - Parkland (Hartmann’s 4ml/kg/%TBSA over 24 hours)
  - Muir and Barclay – which colloid?
  - Other (Please state fluid used and regimen)

**Inhalation Injuries**

1. Always or often  
2. Sometimes or occasionally  
3. Never
**Intensive Care**

*Sedation and Analgesia*

What drugs do you use for sedation and analgesia in ventilated patients?

(Insert 1 if always or often, 2 if sometimes or rarely, 3 if never)

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N°</strong></td>
<td>Midazolam</td>
<td>Propofol</td>
</tr>
<tr>
<td></td>
<td>Haloperidol</td>
<td>Clonidine</td>
</tr>
<tr>
<td></td>
<td>Ketamine</td>
<td>Morphine</td>
</tr>
<tr>
<td></td>
<td>Fentanyl</td>
<td>Alfentanil</td>
</tr>
<tr>
<td></td>
<td>Diamorphine</td>
<td>Methadone</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td></td>
</tr>
</tbody>
</table>

**Colloids** (1 if always or often, 2 if sometimes or rarely, 3 if never)

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Albumin</td>
<td>Dextran</td>
</tr>
<tr>
<td></td>
<td>Gelatin (Gelofusine / Haemaccel)</td>
<td>Hetastarch (Hespan)</td>
</tr>
<tr>
<td></td>
<td>Hexastarch (EloHAES)</td>
<td>Pentastarch</td>
</tr>
<tr>
<td></td>
<td>Voluven</td>
<td></td>
</tr>
</tbody>
</table>

**Muscle Relaxants** (1 if always or often, 2 if sometimes or rarely, 3 if never)

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Atracurium</td>
<td></td>
</tr>
</tbody>
</table>

---

1 Always or often  2. Sometimes or occasionally    3. Never
Cisatracurium
Mivacurium
Pancuronium
Rocuronium
Suxamethonium
Vecuronium
Other ……………………………

Inotropes (1 if always or often, 2 if sometimes or rarely, 3 if never)
Adrenaline
Noradrenaline
Dopamine (Inotrope)
Dopamine (Renal Dose)
Dobutamine
Dopexamine
Other …………………………………

Steroids
Do you ever use corticosteroids in sepsis?

No
1 Always or often  2. Sometimes or occasionally  3. Never

Thromboprophylaxis
Do you routinely assess patients on admission for risk of thromboembolism?    Yes / No
(Delete or circle as appropriate)
If yes, how is this done?
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________

What unfractionated / low molecular weight heparin do you use for thromboprophylaxis?
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________

1 Always or often  2. Sometimes or occasionally  3. Never  359
Stress Ulcer Prophylaxis

In what circumstances is stress ulcer prophylaxis administered?

What drugs (and route) do you use for stress ulcer prophylaxis?

Gut-motility agents
What drugs do you use and at what dose / route?
(Insert 1 if always or often, 2 if sometimes or rarely, 3 if never)

<table>
<thead>
<tr>
<th>Nº</th>
<th>Dose / route</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Metoclopramide</td>
</tr>
<tr>
<td></td>
<td>Erythromycin</td>
</tr>
<tr>
<td></td>
<td>Other</td>
</tr>
</tbody>
</table>

Vitamins, Minerals, Trace Elements

What do you routinely give to your intensive care patients? (Delete / circle as appropriate)

<table>
<thead>
<tr>
<th></th>
<th>Dose / Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascorbic Acid</td>
<td>Yes / No</td>
</tr>
<tr>
<td>Folic Acid</td>
<td>Yes / No</td>
</tr>
<tr>
<td>Iron</td>
<td>Yes / No</td>
</tr>
<tr>
<td>Multivitamin Preparation</td>
<td>Yes / No</td>
</tr>
<tr>
<td>Vitamin B Co</td>
<td>Yes / No</td>
</tr>
<tr>
<td>Zinc</td>
<td>Yes / No</td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
</tbody>
</table>

1 Always or often  2. Sometimes or occasionally  3. Never
Laxatives
Do you routinely give laxatives prophylactically to intensive care patients? Yes / No
What do you use?

<table>
<thead>
<tr>
<th></th>
<th>Yes / No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Senna</td>
<td></td>
</tr>
<tr>
<td>Lactulose</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
</tbody>
</table>

---

Infections and Antibiotics

Do you start blind antibiotic therapy for sepsis (i.e. before cultures isolated) Yes / No
If yes, what is your first-line blind antibiotic treatment? (Please include dose and frequency)

---

Is your antibiotic use influenced by any of the following?

- MRSA Yes / No
- Vancomycin-resistant enterococci Yes / No
- Acinetobacter Yes / No

Other multiple resistant organisms (please state)

---

1. Always or often  2. Sometimes or occasionally  3. Never
Please indicate your usage of antibiotics for three types of infections (1. Often, 2. Sometimes / occasionally, 3. never)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Wound Infections Insert N°</th>
<th>Respiratory Infections Insert N°</th>
<th>Septicaemia Insert N°</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aciclovir</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amikacin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amoxycillin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amphotericin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aztreonam</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzylpenicillin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefotaxime</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftazidime</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefuroxime</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clindamycin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Co-amoxiclav (Augmentin)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colistin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cotrimoxazole</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flucloxacinil</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluconazole</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fusidic Acid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gentamicin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imipenem (Primaxin)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macrolides e.g. erythromycin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meropenem</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metronidazole</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Piperacillin (alone)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Piperacillin with tazobactam (Tazocin)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quinolones e.g. ciprofloxacin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synercid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teicoplanin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ticarcillin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tobramycin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trimethoprim</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other (please state)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 Always or often  2. Sometimes or occasionally  3. Never
All Burns

Wound Care

What wound care products are standardly used on admission for burns wound care?

Full-thickness

Partial thickness

Superficial

Are there any other products that you use?

Please number the following antibacterial products according to your usage
(1 if always or often, 2 if sometimes or rarely, 3 if never)

<table>
<thead>
<tr>
<th>No.</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Flammazine</td>
</tr>
<tr>
<td></td>
<td>Flammacerium</td>
</tr>
<tr>
<td></td>
<td>Silver Nitrate Solution</td>
</tr>
<tr>
<td></td>
<td>Sulphamylon</td>
</tr>
<tr>
<td></td>
<td>Other (please state)</td>
</tr>
</tbody>
</table>

Itching

How do you treat itching in burns?

Pain Control

What drugs have been used for analgesia of non-ventilated patient (excluding intra-operative analgesia)? Insert 1 if always or often, 2 if sometimes or rarely, 3 if never

<table>
<thead>
<tr>
<th>No.</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Paracetamol</td>
</tr>
<tr>
<td></td>
<td>Morphine</td>
</tr>
<tr>
<td></td>
<td>Diamorphine</td>
</tr>
<tr>
<td></td>
<td>Methadone</td>
</tr>
<tr>
<td></td>
<td>Diclofenac</td>
</tr>
<tr>
<td></td>
<td>Ibuprofen</td>
</tr>
<tr>
<td></td>
<td>Clonidine</td>
</tr>
<tr>
<td></td>
<td>Amitriptyline</td>
</tr>
</tbody>
</table>
What is your standard analgesic for dressing changes not under general anaesthesia?

Feeds

What feed type do you use to initiate feeding in major burns?

Adults
Standard 1kcal/ml feed (e.g. Osmolyte, Nutrison Standard, Fresubin) Yes / No
1 kcal/ml fibre-containing feed (e.g. Jevity, Nutrison Multifibre) Yes / No
High energy feed (e.g. Ensure Plus, Nutrison Energy, Fresubin 750) Yes / No
Other (Please specify)

Children
Standard 1kcal/ml feed (e.g. Paediasure, Nutrini, Frebini) Yes / No
1 kcal/ml fibre-containing feed (e.g. Paediasure with Fibre) Yes / No
High energy feed (e.g. Paediasure Plus, Nutrini Extra) Yes / No
Other (Please specify)

How often do you use Total Parenteral Nutrition (TPN), Naso-jejunal (NJ) feeding?

(☐) TPN
Routinely
Sometimes
Rarely
Never

(☐) NJ
Routinely
Sometimes
Rarely
Never

If sometimes or rarely in what circumstances do you use them?
Do you ever use immunonutrition products e.g. glutamine, arginine? Yes / No

If yes, what are your criteria for use?

What route do you use?

Enteral Yes / No

Parenteral Yes / No

Other Drugs

Please tell us about other drugs of interest and in what clinical situations they have been used, for example:
- drugs that are used routinely
- drugs that have been used in difficult cases e.g. epoprostenol
- drugs that have been tried in the past (whether felt to be beneficial or not)
- unlicensed drugs or unlicensed indications for drugs. (Examples include Human Growth Hormone, anabolic steroids, immunoglobulins, topical NSAIDs, beta-blockers.)

Your Details

1 Always or often  2. Sometimes or occasionally  3. Never
May we print these details in the booklet, so that other people can contact you? Y / N

Please return this questionnaire in the envelope provided, as early in January as possible. It would also be useful if you could include any guidelines, protocols etc about anything related to drugs or feeds.

If you have any queries, please contact Jane Allen on 01342 410210 bleep 214 or e-mail jane.allen@qvh-tr.sthames.nhs.uk.

Thank you
Appendix 2. Questionnaire for survey of use of antimicrobial agents in the UK 2009 (Paper version)

Antimicrobial use in major burns patients

We are conducting a survey on antimicrobial use in UK burns units on adult patients with burns > 15% total burns surface area. The purpose of this is to see how much practice varies both on choice of antibiotic and the dose selected.

We intend to publish the results, but individual units will not be identified in any way. This will give you the opportunity to find out what is happening in other units, and help move towards standardising practice (where appropriate) across the UK.

Please could you return this survey by….

<table>
<thead>
<tr>
<th>Trust name:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum number of adult burns ITU beds</td>
<td></td>
</tr>
<tr>
<td>Maximum number of adult burns HDU beds</td>
<td></td>
</tr>
<tr>
<td>Does your trust have antimicrobial guidelines specifically for burns patients?</td>
<td>Y / N</td>
</tr>
<tr>
<td>If yes, would you be willing to share these with us?</td>
<td>Y / N</td>
</tr>
</tbody>
</table>

If yes, please email them to jane.allen@qvh.nhs.uk or post them to:

Jane Allen
Chief Pharmacist
Queen Victoria Hospital NHS Foundation Trust
Holtye Road
East Grinstead
West Sussex RH19 3DZ

If yes, do you give permission for us to share resources and send copies to other units on request?
Please complete for the following antibiotics (write not known or N/A if appropriate). If you never use the antibiotic in major adult burns, please only complete column 2.

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Used? Y / N</th>
<th>On a scale of 1-5, likelihood of using it on a major burn patient 1 = very rarely, 5 = almost certain</th>
<th>Routes used</th>
<th>Usual adult starting dose (for each route)</th>
<th>Main indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aciclovir</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1. blind therapy</td>
</tr>
<tr>
<td>Amikacin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2. only for sensitive organisms</td>
</tr>
<tr>
<td>Amoxycillin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3. on microadvice</td>
</tr>
<tr>
<td>Ampotericin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4. only for MRSA</td>
</tr>
<tr>
<td>Amphotericin (liposomal)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5. Other (please state)</td>
</tr>
<tr>
<td>Aztreonam</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>You may select more than 1</td>
</tr>
<tr>
<td>Benzylpenicillin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Process for deciding dose</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 = local guidelines</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 = burns consultant</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 = microbiologist</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4 = pharmacist</td>
</tr>
<tr>
<td>Cephalosporin oral (name)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5 = junior surgeon</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6 = junior anaesthetist</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7 = consultant</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8 = other (please state)</td>
</tr>
</tbody>
</table>

You may select more than 1 of the above.
<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Used?</th>
<th>Likelihood of using it (1-5)</th>
<th>Routes used</th>
<th>Usual adult starting dose (for each route)</th>
<th>Main indications</th>
<th>Process for deciding dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Y / N</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 = local guidelines</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 = burns consultant</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 = microbiologist</td>
</tr>
<tr>
<td>Clindamycin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4 = pharmacist</td>
</tr>
<tr>
<td>Coamoxiclav</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5 = junior surgeon</td>
</tr>
<tr>
<td>Colistin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6 = junior anaesthetist</td>
</tr>
<tr>
<td>Daptomycin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7 = cons</td>
</tr>
<tr>
<td>Ertapenem</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8 = other (pl state)</td>
</tr>
<tr>
<td>Fluxloxacillin</td>
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<td></td>
<td></td>
<td>You may select more than 1</td>
</tr>
<tr>
<td>Fluconazole</td>
<td></td>
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<td>You may select more than 1</td>
</tr>
<tr>
<td>Gentamicin</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td>You may select more than 1</td>
</tr>
<tr>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td>You may select more than 1</td>
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<tr>
<td>Itraconazole</td>
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<tr>
<td>Linezolid</td>
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<tr>
<td>Meropenem</td>
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<tr>
<td>Metronizazole</td>
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<tr>
<td>Penicillin V</td>
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<tr>
<td>Piperacillin</td>
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<td></td>
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<tr>
<td>Piperacillin &amp; Tazobactam</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Teicplanin</td>
<td></td>
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<td></td>
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<tr>
<td>Ticarcillin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ticarcillin &amp; clavulamic acid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tigecycline</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Valaciclovir</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Vancomycin</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Voriconazole</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Other (state)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
About you

Your job title __________________________________________

Your profession:  Pharmacist  Nurse  Doctor  (surgeon)
Doctor (anaesthetist)  Other (please state)

How long have you been qualified? ________________

How long have you worked on the burns unit? ________________

On average what percentage of your week is spent working with burns patients or burns-related issues? ________________

What is your current grade / banding? ________________

Thank you for completing this questionnaire. Would you like us to send you a copy of the results?

Jane
Appendix 3. Queen Victoria Hospital Burns Centre Antimicrobial Guidelines at start of the study (adapted from intranet web version)

Burns Centre Antimicrobial Guidelines (2002)

Toxic Shock Syndrome (TSS) in Paediatric Burns

TSS is a diagnosis based on a high index of clinical suspicion. No laboratory test is available for confirming the diagnosis of toxic shock syndrome. A significant rise in TSST-1 serum antibody in association with clinical manifestation is strong retrospective support for diagnosis.

Criteria for Diagnosis

- Temperature > 38.9°C
- Erythematous rash
- Hypotension and poor peripheral perfusion

The syndrome also includes signs of systemic upset with renal, hepatic, and gastrointestinal involvement. Neurological deterioration is a late, but very serious complication.

The MARS BAR scoring system has been used to aid diagnosis. Write in the score for each parameter that applies. Use the total score to decide appropriate action (see below).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Score</th>
<th>Patient</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mental State</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irritable / Drowsy</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Hypertonic / Floppy</td>
<td>5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Falling Hb &lt; 9</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Falling platelet count</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Falling WCC &lt; 6.0</td>
<td>5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Alimentary System</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Abdominal Distension</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Renal System</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine Output</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 0.5ml/kg/hour</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macular rash alone</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Core temperature &gt; 40°C</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Rash and temp &gt; 40°C</td>
<td>5</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

TOTAL of first column

TOTAL of second column

TOTAL OF BOTH COLUMNS (Max 44)

Total Score Action
0 – 9 No Treatment
10 – 15 Suspect – close observation
– treat (see next page) if scoring increasing
16 – 25 Highly suggestive – Treat (see below)
> 25 Diagnostic – Treat (see below)
Section 1. Toxic Shock

Treatment
Urgent referral to paediatrician if TSS suspected

Fresh frozen plasma (FFP) or whole blood

Intravenous Flucloxacillin [click here for dose] plus Benzylpenicillin [click here for dose]

or if allergic to penicillin: Intravenous Vancomycin [click here for dose]

Circulatory support as needed

Antibiotic Doses
Flucloxacillin
Dose (Over 1 month)
50mg/kg FOUR times a day. Maximum 8g / day.

Preparation
Add 1.3ml of water for injection to a 250mg vial to give 250mg in 1.5ml, or 1.6ml to a 500mg vial to give 500mg in 2ml. Dilute reconstituted dose to 5-10ml with water for injection.

Administration
IV over 3 – 5 minutes

Benzylpenicillin
Dose (Over 1 month)
50mg/kg FOUR times a day. Maximum dose 14.4g/day.

Preparation
On reconstitution 600mg displaces 0.4ml.

Dissolve 600mg in at least 10ml sodium chloride 0.9%.

Administration
IV infusion over at least 30 minutes

Vancomycin
Dose
20mg every TWELVE hours by intermittent infusion (Maximum initial dose usually 1g every TWELVE hours)

Preparation
On reconstitution 500mg displaces 0.3ml. Add 9.7ml of water for injection to the 500mg vial to give a 50mg in 1ml solution, then dilute with either sodium chloride 0.9% or glucose 5% to a concentration not exceeding 5mg/ml e.g. 500mg in 100ml.

Administration
Intermittent intravenous infusion at a rate not exceeding 10mg/minute (i.e. 500mg over 50 minutes)

Monitoring
See vancomycin intermittent infusion guidelines [click here]
Section 1. Toxic Shock

Minor Burns (<15% TBSA Adult or <10% TBSA Child)

Treatment of Burn Site Infections (Cellulitis)

Check if there are any swab results. If so, treat accordingly, or discuss with microbiologist if unsure. Otherwise choose the option below that applies:

<table>
<thead>
<tr>
<th>Has the patient been in hospital for more than 72 hours at any time since burn occurred?</th>
<th>Is the patient a known MRSA carrier?</th>
<th>Is the patient allergic to penicillin?</th>
<th>Recommended antibiotic therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Flucloxacillin i.v. ([click here for adult dose]) plus benzylpenicillin i.v. ([adult dose])</td>
</tr>
<tr>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Vancomycin intermittent infusion ([adult dose]) or clindamycin oral / iv ([adult dose])</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>Yes or No</td>
<td>Vancomycin intermittent infusion ([adult dose])</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Tazocin i.v. ([adult dose])</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Vancomycin intermittent infusion ([adult dose]) plus oral ciprofloxacin ([adult dose])</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>Yes or No</td>
<td>Vancomycin intermittent infusion ([adult dose]) plus oral ciprofloxacin ([adult dose])</td>
</tr>
</tbody>
</table>

For all other types of infection in patients with minor burns, consult the Trust’s “Guidelines for the use of Antimicrobial Agents”.

Ensure swabs and cultures are taken before starting antibiotic therapy.

Antibiotic Doses

The doses below are for adults with normal renal function. If infections are severe or life-threatening, higher doses may be needed (see BNF). See the general prescribing guidelines section for children’s doses.

- **Benzylpenicillin**
  - Intravenous: 1.2g every SIX hours

- **Ciprofloxacin**
  - Oral: 500mg or 750mg every 12 hours

- **Clindamycin**
  - Oral: 300mg or 450mg every SIX hours
  - Intravenous: 300mg to 600mg every six hours

- **Flucloxacillin**
  - Intravenous: 1g every SIX hours

- **Tazocin**
  - Intravenous: 4.5g every EIGHT hours
Vancomycin traditional dosing by intermittent infusion

Adult Dose
Usually 1g intravenously every 12 hours, ideally at 10am and 10pm. A lower dose may be required for elderly or lightweight patients. The dose should be reduced for patients with impaired renal function

Preparation
Each 500mg vial should be reconstituted with 10ml of Water for Injection. A 1g dose should usually be added to at least 200ml Sodium Chloride 0.9% or Dextrose 5% for a maximum concentration of 5mg/ml. If fluid restricted 1g can be infused centrally in a volume of 100ml (10mg/ml), but this may increase the risk of infusion-related events.

Administration
The maximum rate of administration is 10mg / minute. Therefore 1g should be given over at least 100 minutes. If possible, the sites of infusion should be rotated.

Drug Level Monitoring
On the third or fourth dose, a trough level should be taken (i.e. immediately before the dose is given) together with U&Es. The level should be 5 – 15mg/L. The trough level should be rechecked on the third or fourth dose after a dose change. If no dose adjustment is necessary and the patient is stable, levels and U&Es can be checked every three days.

Duration of Treatment
The minimum length of treatment for MRSA is usually five days. For a venflon site, CVP site or blood culture isolate, treatment should be for at least ten days. If in doubt, ask.

Compatibility Y-site compatible with aciclovir, fluconazole, morphine
Major Burns
For treatment of infections of all adult burns 15% and over total body surface area (TBSA) or children 10% and over TBSA, contact microbiologist (see below). Please ensure swabs and cultures are taken before starting antibiotic therapy.

Consultant Microbiologists
The consultant microbiologists for the Queen Victoria Hospital are based at the Surrey and Sussex NHS Trust: Dr B. Stewart at East Surrey tel **17 ext 1698, or consultant microbiologist at Crawley Hospital tel **16 ext 3093

Doses, Administration and Monitoring
Recommended doses of antibiotics in patients with major burns may vary from standard doses, please consult the following guidelines.

Amikacin
- **Adult Dose:** Non life-threatening infections (other than pseudomonal infections): 7.5mg / kg intravenously every twelve hours (equivalent to 500mg twice a day in adults), ideally at 10am and 10pm.
- Life-threatening infections and / or those caused by Pseudomonas, the adult dose may be increased to 500mg every eight hours, but should usually neither exceed 1.5g/day nor be administered for a period longer than 10 days. A maximum total adult dose of 15g should not be exceeded.
- Lower dose or longer dose interval in renal impairment (see package leaflet or contact pharmacy for advice).

Preparation
- Dilution is not normally necessary, but may be diluted with 10 – 20ml sodium chloride 0.9% or glucose 5%.

Administration
- Slow i.v. injection over 3 - 5 minutes.

Drug Level Monitoring
- Take levels before and after the 3rd or 4th dose. Immediately before dose (trough) should be less than 10mg/L. One hour post-dose (peak) 20 - 30mg/L.

Compatibility
- Amikacin may be added to a metronidazole infusion bag. Y-site compatible with ranitidine.

Ceftazidime
- **Adult Dose:** 2g intravenously every EIGHT hours. Lower dose or longer dose interval in renal impairment.

Preparation
- To reconstitute each 1g vial, inject 10ml Water for Injection and shake to dissolve. The vials may contain a vacuum to assist injection of the diluent. Carbon dioxide is released as the antibiotic dissolves, generating pressure within the vial. The solution will become clear within 1 to 2 minutes. Invert the vial and completely depress the syringe plunger prior to insertion. Insert the needle through the vial stopper. Be sure the needle remains within the solution and withdraw the contents of the vial in the usual manner. Pressure in the vial may aid withdrawal. The withdrawn solution may contain carbon dioxide bubbles, which should be expelled from the syringe before injection.

Administration
- Slow i.v. injection over 3 – 5 minutes

Compatibility
- Ceftazidime may be added to a metronidazole infusion bag. Y-site compatible with aciclovir, heparin, hydrocortisone sodium succinate and potassium chloride.

Note
- The development of a positive Coomb’s test associated with the use of ceftazidime in 5% of patients may interfere with the cross-matching of blood.

Ciprofloxacin
- **Adult Dose:** 400mg intravenously every EIGHT hours. (This is higher than the usual recommended dose of 400mg every 12 hours.) Reduce dose in renal impairment if creatinine clearance is less than 20ml/min

Preparation: Ready-prepared bags of 400mg in 200ml

Administration: Infuse 400mg i.v. over 60 minutes.

Compatibility
- Y-site compatible with dopamine, digoxin, gentamicin, metronidazole and potassium chloride.
Colistin
Intravenous
Adult Dose (over 60kg)
2 million units by intravenous infusion every EIGHT hours. Lower dose or longer dose interval in renal impairment.

Preparation
Reconstitute each vial with 10ml Water for Injection or Sodium Chloride 0.9%, then dilute further with sodium chloride 0.9% or glucose 5%. Usual final volume 50 – 100ml.

Administration
Intravenous Infusion over 30 – 60 minutes

Compatibility
Do not infuse with other drugs

Nebules
Adult Dose
2 million units every EIGHT hours. Administer each dose after a salbutamol nebule to prevent bronchospasm.

Preparation
It is advisable to reconstitute as close as possible to the osmolarity of physiological saline. To make up 2 megaunits in 4ml, draw up 1.5ml of sodium chloride 0.9% and 2.5ml Water for Injection into one syringe and use this for reconstituting the two vials. Take the cap and bung off each vial and add 2ml of solution. Dissolve the powder, then pour into the nebuliser. See package insert for further information, or if volume of less than 4ml required.

Administration
The nebuliser should produce droplets of 5 microns or less and should have an effective filter on the ventilator side of the expiratory tube to ensure exhaled antibiotic is not discharged into the room. Air flow rate should be 8 to 10 litres / minute.

Compatibility
Gentamicin may be mixed with colistin if time factor is crucial; add the gentamicin dose to the colistin dose vial immediately before use and then make up to 3ml with Sodium Chloride 0.9%.

Nebuliser Care
Drug company guidelines are kept in each ITU drug file. A copy can also be obtained from Medicines Information, ext 210.

Gentamicin
Intravenous

Adult Dose
It is not appropriate to use “Once Daily” administration in Burns
The following table gives recommended intravenous starting doses for patients with normal renal function.

<table>
<thead>
<tr>
<th>Age</th>
<th>Total Daily Dose (mg / kg / day)</th>
<th>Dosing interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>11 – 30</td>
<td>7.5</td>
<td>6 hourly</td>
</tr>
<tr>
<td>31 – 60</td>
<td>5</td>
<td>8 hourly</td>
</tr>
<tr>
<td>over 60</td>
<td>3</td>
<td>12 hourly</td>
</tr>
</tbody>
</table>

Patients with poor renal function
The total daily dose should be decreased and the dosing interval increased according to severity.

Preparation
Dilution is not normally necessary, but may be diluted with Sodium Chloride 0.9% (usually 10 – 20ml)

Administration
Slow i.v. injection over 2 – 3 minutes.

Drug Level Monitoring
Levels can usually be taken by the third dose (immediately before and 15 minutes after)

Optimum levels: Peak 5 - 10 mg/L
(For severe infection aim for at least 8mg/ml)

Trough Less than 2.0 mg/L
If a dose change is necessary, check levels again 24 hours later. If no change is needed, levels can be checked every three days, provided renal function is stable.

**Compatibility**
‘Y-site compatible with atracurium, ciprofloxacin, insulin and metronidazole

**Nebulised**

**Adult Dose**
80mg every TWELVE hours, usually after bronchodilators e.g. salbutamol

**Preparation**
Make up to 3ml with sodium chloride 0.9%.

**Administration**
The nebuliser should have an effective filter on the ventilator side of the expiratory tube to ensure exhaled antibiotic is not discharged into the room.

**Compatibility**
May be mixed with colistin if time factor is crucial; add the gentamicin dose to the colistin dose vial immediately before use and then make up to 3ml with sodium chloride 0.9%.

**Imipenem with Cilastatin (Primaxin®)**

**Adult Dose**
Imipenem 50mg/kg/day in 3 or 4 divided doses. Maximum 4g in 24 hours. Lower dose or longer dose interval in renal impairment.

**Preparation**
Each 500mg vial should be reconstituted with 100ml of sodium chloride 0.9% or glucose 5%. See package insert for further instruction.

**Administration**
Infuse 1g i.v. over 40 – 60 minutes

**Compatibility**
‘Y-site compatible with aciclovir

**Linezolid**

**Adult Dose**
600mg intravenously every TWELVE hours

**Preparation**
Ready-prepared bags of 600mg in 300ml

**Administration**
Infuse over 30 to 120 minutes

**Compatibility**
Do not infuse with any other drugs.

**Meropenem**

**Adult Dose**
1g intravenously every eight hours. A dose of 2g every eight hours is recommended for severe infections such as meningitis and for cystic fibrosis. Lower dose or longer dose interval in renal impairment.

**Preparation**
Reconstitute 1g of meropenem with 20ml Water for Injections.

**Administration**
Usually slow i.v. injection over 5 minutes.

**Compatibility**
Do not infuse with other drugs

**Tazocin® (Piperacillin and Tazobactam)**

**Adult Dose:** 4.5g every SIX hours. Lower dose or longer dose interval in renal impairment.

**Preparation:** Each 4.5g vial should be reconstituted with 20ml of Water for Injection or sodium chloride 0.9%.

**Administration:** Usually slow i.v. injection over 3 - 5 minutes.

**Compatibility:** ‘Y-site compatible with potassium chloride
**Teicoplanin**

**Adult Dose**
12mg/kg intravenously every 12 hours for the first three doses, then 12mg/kg once a day. (NB This is twice the normal recommended dose). For the average adult patient (70kg) the 12mg/kg dose can be rounded off to 800mg (2 x 400mg vials). Lower doses may be required in patients with renal failure.

**Preparation**
The entire contents of the water ampoule (in the injection box) should be slowly added to the vial. Do not shake the vial, but roll it gently until the powder is completely dissolved, taking care to avoid formation of foam. If the solution does become foamy, allow to stand for 15 minutes for the foam to subside. The injection can be diluted further with sodium chloride 0.9% or glucose 5%.

**Administration**: Slow I.V. injection over 3 – 5 minutes.

**Drug Level Monitoring**
On the fourth day, a trough level should be taken immediately before the dose is due, plus a peak level one hour after. Trough levels should be at least 15mg/L (higher than usually recommended) and the peak should normally be less than 50mg/L.

**Compatibility**
Do not infuse with other drugs

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**Vancomycin by continuous infusion**
(Adapted from guidelines from Guy’s and St Thomas’ Hospital NHS Trust)

Continuous infusion vancomycin should be used for all intensive care burns patients and all other burns patients with severe infections.

**Background**
The efficacy of vancomycin depends on the time for which the serum concentration exceeds the minimum inhibitory concentration for the micro-organism rather than the attainment of high peak concentrations. There is evidence that giving vancomycin as a continuous infusion over 24 hours is as effective as the traditional method of intermittent infusions whilst being much simpler to organise in terms of monitoring serum levels.

**Prescribing**

**Loading dose**
All patients should receive a weight-related loading dose.

< 65kg: 1g IV over 1hr

> 65 kg: 1.5g IV over 1 hr

**Continuous Infusion**
The continuous intravenous infusion should follow straight after the loading dose and be based on an estimate of the patient’s age and renal function (see table below)

<table>
<thead>
<tr>
<th>Estimated creatinine clearance (ml/min)</th>
<th>Starting daily vancomycin dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal renal function under 60 years</td>
<td>40mg/kg (rounded off to nearest 500mg)</td>
</tr>
<tr>
<td>Normal renal function over 60 years</td>
<td>35mg/kg (rounded off to nearest 500mg)</td>
</tr>
<tr>
<td>Mild impairment 20-50</td>
<td>Reduce dose for normal renal function by 500mg</td>
</tr>
<tr>
<td>Moderate impairment 10-20</td>
<td>Reduce dose for normal renal function by 1g</td>
</tr>
<tr>
<td>Severe impairment &lt; 10</td>
<td>Reduce dose for normal renal function by 1.5g</td>
</tr>
<tr>
<td>Filtration /Diafiltration</td>
<td>Reduce dose for normal renal function by 1g</td>
</tr>
</tbody>
</table>
Administration
Loading dose: Vancomycin 1g or 1.5g in 100 mL sodium chloride 0.9% over one hour via a central line

Continuous Infusion
For central administration - make up vancomycin each 500 mg in at least 50 mL sodium chloride 0.9%

For peripheral administration - allow at least 100 mL sodium chloride 0.9% for every 500 mg of vancomycin

Monitoring Levels
Request a serum level each morning (ideally between 8am and 9am). If treatment with vancomycin is started 4 hours or less before the morning level is due, wait for the next morning’s level to adjust the dose

The daily dose should be adjusted according to the level

<table>
<thead>
<tr>
<th>Vanc level</th>
<th>Dosage required</th>
<th>change</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 15 mg/L</td>
<td>Increase the dose by 500mg</td>
<td></td>
</tr>
<tr>
<td>15 – 25 mg/L</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td>25.1 – 30 mg/L</td>
<td>Decrease the dose by 500mg*</td>
<td></td>
</tr>
<tr>
<td>&gt; 30 mg/L</td>
<td>Stop infusion for 6hrs. Restart at a reduced dose</td>
<td></td>
</tr>
</tbody>
</table>

*If the patient is only receiving 500 mg/day, the dose should be decreased to 250 mg /day

Y-site Compatibility
Whenever possible give via a separate lumen
Vancomycin at this concentration (10 mg/ml) has y-site compatibility with propofol and fluconazole. At lower concentrations (5mg/ml), y-site compatibility with atracurium, amiodarone, magnesium sulphate, midazolam, morphine and vecuronium.

References

Individual Drug Summaries of Product Characteristics
Royal College of Paediatrics and Child Health Medicines for Children 1999
Paediatric formularies.

Pharmacy Department
Appendix 4. Meropenem HPLC studies

Aim and objectives
As discussed in chapter 3, the primary aim of the HPLC analysis was to determine the stability of meropenem in whole blood and serum.
The objectives were to:
  - confirm the accuracy and reproducibility of the assay both in water and in serum
  - determine the stability of meropenem in whole blood and if this was found to be less than 95% at 24 hours, to confirm that that meropenem was stable in serum.

Materials and Methods

Initial studies were in water. The HPLC method used was based on Elkhaili et al (1996).
Briefly:
0.25ml plasma mixed with an equal volume of acetonitrile in an eppendorf.
Vortex for 10 minutes
Centrifuge for 10 mins at 1000g
Transfer supernatant to another 1.5ml eppendorf.
Add 0.5ml methylene chloride
Vortex for 5 minutes
Centrifuge for 10 mins at 1000g
Inject 20microlitre onto column.
The HPLC details were as follows:
Waters 717 plus autosampler
Perkin Elmer series IC pump
Shimadzu SPD-6A UV Spectrophotometric detector
Shimadzu CR5A Chromatopac recorder
Water Column 4.6 x 150mm

Two stock solutions were used and from each of these, concentrations of 2mg/L, 10mg/L, 20mg/L, 50mg/L, 100mg/L and 200mg/L were prepared. Serum samples from healthy volunteers were also spiked at 1mg/L, 10mg/L and 100mg/L. Solutions of the other compounds used in the process were also prepared to enable the meropenem peak to be identified.
Whole blood samples (10ml) were taken from healthy volunteers who were not receiving meropenem. To enable this, the volunteers were given an information leaflet explaining the study and the need for samples from volunteers. Written consent was then obtained. Samples were taken at the Queen Victoria Hospital by the phlebotomist.

For studies in whole blood, heparinised tubes were used to prevent clotting occurring (Vacutainer®). These were then spiked with meropenem to achieve three concentrations (1mg/L, 10mg/L and 100mg/L). When ready for analysis, the samples were transferred to serum gel tubes (Vacutainer®), which were then centrifuged at 2000g for 15 minutes, before transferring the supernatant with a glass pipette.

For studies in serum, samples were placed immediately into serum gel tubes, which were then centrifuged at 2000g for 15 minutes. After transfer of the supernatant, samples were spiked with meropenem.

The stability of meropenem in whole blood, when stored at 2 to 8°C was determined. Two samples each of meropenem in whole blood, 1mg/L, 10mg/L and 100mg/L, were stored in the fridge. They were analysed at 24 hours and then 3, 5 and 7 days. If it was found that there was more than 5% degradation after 24 hours, stability of meropenem in serum would be confirmed.
Results

At a wavelength of 298nm, and a flow rate of 1.25ml/hour, the meropenem peak appeared at 5.2 minutes (Figure 1). A peak was not seen at this time with the solutions that did not contain meropenem.

Figure 1. HPLC of solutions of meropenem in water and serum, serum alone, methylene chloride and acetonitrile.

The largest peak, at 5.2 minutes, is only seen with the solutions containing meropenem.

Solutions of meropenem in both serum and aqueous solution showed a linear relationship ($R^2 > 0.999$) between area under the curve (AUC) and concentration (Figure 2)
In whole blood there was degradation of more than 5% after 24 hours at 4°C. Degradation was greatest (10%) with the 1mg/L solution and least (7%) with the 100mg/L solution. Degradation was logarithmic (Figure 3).
As meropenem was found not to have sufficient stability in whole blood, stability in plasma at 4°C was confirmed to be 95% at 48 hours.

Reference
Appendix 5. Analysis of colistin

Published methods HPLC analysis
As the microbiological assay was not able to differentiate between colistimethate sodium and colistin, it was decided to follow the HPLC methods published by Li et al (2001 and 2002) to determine whether the method could be reproduced. These methods were selected as they were the only ones that differentiated between colistin and colistimethate sodium, colistin A and B, and partial sulfomethyl derivatives.

Outline of HPLC colistin method (Li et al. 2001a)
Colistin cannot be detected by UV detection. Therefore it is necessary to derivatise the sample and use a fluorescence detector.

Plasma sample pre-treatment
An internal standard of netilmicin was mixed with serum containing colistin sulphate. After adding a mixture of methanol and trichloroactic acid, the tube was vortexed and centrifuged.

The supernatant was then transferred to another tube and mixed with sodium hydroxide solution, before adding methanol-hydrochloric acid. The final solution was then delivered to a conditioned SPE cartridge.
Derivatisation

The SPE cartridges were conditioned with methanol and equilibrated with carbonate buffer, by using a vacuum manifold and without allowing the cartridges to run dry.

All of the final pre-treatment solution was transferred to the cartridge. After washing with carbonate buffer, the derivatising agent, FMOC-Cl in acetonitrile, was added. Following 10 minutes of reaction, the cartridge was dried by drawing air through under vacuum. The derivatives were then eluted with acetone and the eluate mixed with boric acid solution.

HPLC analysis

A mobile phase made up of acetonitrile-tetrahydrofuran-water was used with fluorescence detection at an excitation wavelength of 260nm and an emission wavelength of 315nm. Two major peaks were detected; firstly colistin B and the colistin A.

Outline of colistimethate sodium method (Li et al 2002)

To quantify colistin and colistimethate sodium (CMS) separately, it was necessary to split the sample. One part (a) was run as for Li et al (2001) and the other (b) involved accelerated hydrolysis followed by extraction and derivatisation as above. This ensured that all of the CMS was hydrolysed to colistin. By subtracting (a) from (b), the original concentration of CMS could then be determined. The method therefore did not differentiate between fully and partially sulfomethylated derivatives of CMS in the sample.

For the accelerated hydrolysis, the plasma sample was mixed with netilmicin as the internal standard. Sulphuric acid was then added to accelerate the hydrolysis. After ten minutes, sodium hydroxide was added to stop the reaction.

Pre-treatment, derivatisation and HPLC analysis were then carried out as for 1.1.

Peaks for colistin A appeared at around 14 minutes, colistin B at 12 minutes. The identity of the colistin derivatives were confirmed by mass spectral analysis.
Reproducing the HPLC methods

Derivatisation of colistin was undertaken to confirm linearity between concentration and area under the curve,

Standards of colistin sulphate were made up in acetone:boric acid 0.2\textit{M} (3:2) the following strengths: 0.1, 1, 5, 10, 50 and 100\textit{μ}g/mL, plus blank (no colistin)

1mL of each strength
Add 30\textit{μ}L FMOC-Cl 100m\textit{M} in acetonitrile
Leave for 10 minutes to derivatise
Inject samples

\textbf{HPLC}
Mobile phase \textit{acetonitrile-tetrahydrofuran-water (50:30:20)}
Rate 1.5mL/min
Run time 20 minutes
Temp 25°C
Recorder Shimadzu C-RSA Chromatopac
Autosampler Waters 717 Plus
Pump Perkin Elmer Series 200 IC
Detector Varian Prostar Fluorescence
Wavelength Excitation 260nm, emission 315nm
Column Genesis C18 120A 4\textit{μ}
Injection Volume 10\textit{μ}L

As the initial FMOC peak was large, the method was repeated using only 5\textit{μ}L of FMOC-Cl, to see if this reduced the size of the initial peak.

The method was repeated but adding 10\textit{μ}L of glycine 0.1\textit{M} 10 minutes after the FMOC-Cl, to “kill” the reaction

There was no correlation between the areas under the curve for what was thought to be colistin A and B and the concentration of colistin used (Tables 1a and c, Figures 1a and b).
### Table 1a Peaks detected thought to be colistin A

<table>
<thead>
<tr>
<th>Concentration</th>
<th>FMOC 30 Time</th>
<th>AUC</th>
<th>FMOC 5 Time</th>
<th>AUC</th>
<th>FMOC5 + glycine Time</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1 mcg/ml</td>
<td>ND</td>
<td>ND</td>
<td>13.7</td>
<td>2390</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>1 mcg/ml</td>
<td>13.2</td>
<td>478</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>5 mcg/ml</td>
<td>13.2</td>
<td>43349</td>
<td>13.5</td>
<td>19322</td>
<td>13.4</td>
<td>30303</td>
</tr>
<tr>
<td>10 mcg/ml</td>
<td>13.1</td>
<td>12544</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>50 mcg/ml</td>
<td>13.3</td>
<td>11901</td>
<td>13.5</td>
<td>9483</td>
<td>13.4</td>
<td>14380</td>
</tr>
<tr>
<td>100 mcg/ml</td>
<td>13.2</td>
<td>47280</td>
<td>13.4</td>
<td>23043</td>
<td>13.4</td>
<td>14693</td>
</tr>
</tbody>
</table>

ND = not detected

### Table 1b Peaks detected thought to be Colistin B

<table>
<thead>
<tr>
<th>Concentration</th>
<th>FMOC 30 Time</th>
<th>AUC</th>
<th>FMOC 5 Time</th>
<th>AUC</th>
<th>FMOC5 + glycine Time</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1 mcg/ml</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>1 mcg/ml</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>5 mcg/ml</td>
<td>11.4</td>
<td>13985</td>
<td>11.7</td>
<td>5442</td>
<td>11.5</td>
<td>9957</td>
</tr>
<tr>
<td>10 mcg/ml</td>
<td>11.5</td>
<td>22254</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>50 mcg/ml</td>
<td>11.4</td>
<td>2428</td>
<td>11.6</td>
<td>2465</td>
<td>11.6</td>
<td>3948</td>
</tr>
<tr>
<td>100 mcg/ml</td>
<td>11.4</td>
<td>5638</td>
<td>11.6</td>
<td>4862</td>
<td>11.5</td>
<td>10433</td>
</tr>
</tbody>
</table>
Figures 1a and b. Area under the curve vs concentration of colistin A and B using FMOC 30μl, 5μl and FMOC 5μL plus 10μL of glycine 0.1\textit{M} 10 minutes added after the FMOC-Cl

Blanks (no colistin) were run for each part of this experiment. When FMOC was used without glycine, there was one initial peak which had not returned to zero by 20 minutes. When the glycine was used with 5μL of FMOC-Cl, peaks were detected at 13.3 and 14.9 minutes (Table 2).
Table 2. AUC for blank solutions without colistin.

<table>
<thead>
<tr>
<th></th>
<th>Time</th>
<th>AUC</th>
<th>Time</th>
<th>Peak area</th>
</tr>
</thead>
<tbody>
<tr>
<td>FMOC 30</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FMOC 5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FMOC 5 + glycine</td>
<td>13.3</td>
<td>5584</td>
<td>14.9</td>
<td>34254</td>
</tr>
</tbody>
</table>

Adapting the method
Volume of FMOC-Cl required to derivatise the sample.

The results from 1.3 showed no correlation between colistin concentration and peak area. It was thought that this could be due to the sample not being fully derivatised. The next experiment was therefore to determine the optimum volume of FMOC-Cl to fully derivatise the colistin.

20μL of standard (100μg/mL colistin in water) mixed with 1% carbonate buffer* and FMOC-Cl* (1.0mM in acetonitrile) and left to react for 10 minutes.
Add 30μL glycine (0.1M) and leave for 2 minutes.
Add 600μL boric acid solution (0.2M)

* B 500μL FMOC and 500μL carbonate buffer, but no colistin
S1 500μL FMOC and 500μL carbonate buffer
S2 400μL FMOC and 600μL carbonate buffer
S3 300μL FMOC and 700μL carbonate buffer
S4 200μL FMOC and 800μL carbonate buffer
S5 As for S1, but using colistin in acetone:boric acid 0.2M 3: 
B2 As for blank but fresh solutions

Injection volume 10μL
Run time 16 minutes
Temperature 25°C
Chart recorder Width 50, slope 100, min area 10, speed 4, method 042. All others at default values.
Other HPLC details as for 1.3.1

S1 to S4 was repeated to determine reproducibility. On the second run, fresh solutions were used.

Although the peak areas vary with the amount of FMOC, there appeared to be no correlation between the two (table 3). The optimal volume of FMOC could not therefore be determined.

Table 3. Area under curve relating to colistin A and colistin B using different concentrations of FMOC.

<table>
<thead>
<tr>
<th></th>
<th>First run</th>
<th></th>
<th>Second run</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time</td>
<td>–Time</td>
<td>–Time</td>
<td>–Time</td>
</tr>
<tr>
<td></td>
<td>11.4 mins</td>
<td>13.2 mins</td>
<td>11.6 min</td>
<td>13.8 – 16 min</td>
</tr>
<tr>
<td>Colistin B</td>
<td>11.6 mins</td>
<td>-13.5 mins</td>
<td>-13.5 min</td>
<td></td>
</tr>
<tr>
<td>Colistin A</td>
<td>13.2 mins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blank</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S1 500 µL FMOC</td>
<td>14319</td>
<td>55307</td>
<td>ND</td>
<td>1622</td>
</tr>
<tr>
<td>S2 400 µL FMOC</td>
<td>39257</td>
<td>144840</td>
<td>18433</td>
<td>71147</td>
</tr>
<tr>
<td>S3 300 µL FMOC</td>
<td>18134</td>
<td>69912</td>
<td>18585</td>
<td>44256</td>
</tr>
<tr>
<td>S4 200 µL FMOC</td>
<td>56966</td>
<td>194032</td>
<td>5939</td>
<td>27357</td>
</tr>
<tr>
<td>S5 500 µL FMOC in acetone / boric acid</td>
<td>37313</td>
<td>112666</td>
<td>7554</td>
<td>29958</td>
</tr>
<tr>
<td>Blank 2</td>
<td>27239</td>
<td>98004</td>
<td>Not repeated</td>
<td>Not repeated</td>
</tr>
<tr>
<td></td>
<td>12069</td>
<td>50232</td>
<td>ND</td>
<td>1463</td>
</tr>
</tbody>
</table>

Peaks at colistin times for the blanks could not be explained. It is also noted that on the second day, only the later colistin peak was seen with the blank. The results were also not reproducible (Figures 2a and b).
Individual components
Each of the components were run separately on the HPLC (Table 4). This could show any peaks appearing at colistin times in the blank samples. HPLC details and concentrations used before.

The addition of the FMOC could explain the later peak detected in the blank samples without colistin.
Table 4. HPLC of individual components of colistin analysis

<table>
<thead>
<tr>
<th>Component</th>
<th>Peak time</th>
<th>Peak area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbonate buffer</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>FMOC</td>
<td>13.9</td>
<td>2751</td>
</tr>
<tr>
<td>Glycine</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Boric acid</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Carbonate + FMOC</td>
<td>15.3</td>
<td>6529</td>
</tr>
<tr>
<td>Carbonate + FMOC + glycine</td>
<td>15.3</td>
<td>1922</td>
</tr>
<tr>
<td>Full blank (Carbonate, FMOC, glycine and boric acid)</td>
<td>15.4</td>
<td>2962</td>
</tr>
</tbody>
</table>

In case there were further peaks after 18 minutes, a full standard (with colistin) was run for 40 minutes. Nothing was detected after 16 minutes. A blank was then rerun for 20 minutes. A peak of similar size peak to the original blank was seen at 15.41 minutes.

Effect of glycine volume

As glycine is included in the method to “kill” the FMOC, it was decided to see if the volume used had any effect on the peak area.

20μL 100μg/mL colistin, 500μL 1% carbonate buffer, 500μL 1.0mM FMOC
Leave for 10 minutes
Add 0.1M glycine (see volumes below).
Leave for 2 minutes
Add 600μL of 0.2M boric acid

G1  30μL glycine
G1  40μL glycine
G2  50μL glycine
G3  60μL glycine
No correlation was found between the concentration of glycine and peak area, although a similar pattern was seen for colistin A and B (Figure 3).

Figure 3. Effect of different volumes of glycine 0.1 \( M \).

Concentration of sample, amount of FMOC and amount of glycine

It appeared that the quantity of both FMOC and glycine may have affected the peak area for a given concentration of colistin, although the relationship was not linear, and results did not appear to be reproducible. Eighteen samples were prepared to further address the concentration of colistin, amount of FMOC and amount of glycine (Table 5).

Other than sample 5, no peaks were seen around the colistin times for all of the samples where 20μl of 1μg/mL samples of colistin was added. Small peaks were seen with sample 5, although times were later than the other samples. As 20μL of 1μg/mL was added to a total volume of 1.6ml, the colistin concentration in the sample analysed was 0.0124μg/mL. Therefore it was not surprising that nothing could be detected.
Table 5. The effect of colistin, FMOC and glycine

<table>
<thead>
<tr>
<th>Sample number</th>
<th>Colistin (μg/mL) (20μL)</th>
<th>FMOC 100mM (μL)</th>
<th>Glycine 0.1M (μL)</th>
<th>Time</th>
<th>Peak area</th>
<th>Time</th>
<th>Peak area</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>5</td>
<td>0</td>
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<td>ND</td>
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<tr>
<td>2</td>
<td>1</td>
<td>10</td>
<td>0</td>
<td>ND</td>
<td>ND</td>
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<td>ND</td>
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<td>3</td>
<td>1</td>
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<td>ND</td>
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<td>17</td>
<td>100</td>
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<td>18</td>
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<td>40</td>
<td>13</td>
<td>12355</td>
<td>15.2</td>
<td>41943</td>
</tr>
</tbody>
</table>

ND no peaks detected between 10 and 18 minutes. All samples contained 1ml of carbonate buffer 1% and 600μl of boric acid 0.2M. Total volume 1.6ml.

The effect of FMOC, without glycine, appeared to be maximal between 10 and 20μl for the peaks thought to be colistin A and B (Figure 4), although this was more apparent with peaks thought to be from colistin A, than those thought to be of colistin B. When glycine was added, it appeared that the lower volume (20μl of 0.1 M) resulted in larger peaks than the higher volume (40μl).
Figure 4 The effect of FMOC concentration

All samples contained 20μl of colistin 100μg/ml, 1ml of carbonate buffer 1% and 600μl of boric acid 0.2M and no glycine.
Discussion

The HPLC assay of colistin based on the method by Li et al. (2001a) could not be reproduced. For this reason, no attempt was made to follow the method for colistimethate sodium (Li et al. 2002). Colistin standards were derivatised with FMOC-Cl, for detection by fluorescence detector. Whilst this did give peaks which were thought to correspond to colistin A and B for most samples, there was no relationship between the concentration of colistin used and peak areas. Reduction of the amount of FMOC (to give a narrower first peak) and the use of glycine to “kill” the FMOC reaction did not improve results.

It was thought possible that optimum quantity of FMOC had not yet been found. Therefore different quantities of FMOC with one concentration of colistin were tested. Each sample gave different peak areas, but there appeared to be no relationship between the amount of FMOC used, and the peak areas. Additionally, when the experiment was repeated, the results could not be reproduced.

In addition to the difficulties of the colistin detection, at times the blank samples without colistin had one or two peaks around the times expected for colistin A and B. Therefore each individual component was run through the HPLC separately. It appeared that FMOC could give a peak at around 15 minutes, which could therefore be affecting the peak area when the colistin standards are run. In the method by Li et al. excess FMOC is removed before analysis, which may explain why they had more consistent results. However, in the first experiment, no peaks were seen with the FMOC blanks, until the glycine was added when two peaks were seen. This may have been due to contamination of the blanks.

The effect of FMOC and glycine were further investigated. This time the quantities of FMOC were of a similar range to both the first experiment and the method by Li et al. It was seen that the amount of FMOC made little difference to the peak area corresponding to colistin B, but had some effect on the colistin A peak. The larger the volume of glycine used, the smaller the peak area. This could reinforce the earlier work which suggested that the peaks thought to be colistin A and B are, at least in part, due to unreacted FMOC.

One variable that was not investigated was whether ten minutes was sufficient time for the FMOC derivatisation. If the reaction was not complete in this time it could explain why
results were so inconsistent. In the Li paper, after ten minutes excess FMOC was removed.

In summary, a linear relationship between concentration of colistin and peak areas could not be established. Some blank samples gave peak areas at times expected for colistin, which was thought may have been due to excess FMOC. The use of glycine may have a detrimental effect to colistin peak areas and was not used in the Li HPLC method.

Because of the difficulties with reproducing the assay, it was decided to use the microbiological assay method for the pharmacokinetic study, as this could be undertaken by an accredited service, so allowing quick turnaround and using an established method.

References


Appendix 6. Sheet used by nursing staff to ensure accurate timing and recording of the taking of blood samples.

Meropenem sampling – Date / Patient’s Name / Hospital Number

Approximately 3ml is required in gold lidded serum gel tubes.

Exact time of previous midnight dose of meropenem _______ given over _____ mins

1st sample: Just before 8am dose: Exact time ______________ by _______

8am dose of meropenem: Exact time given : ___________ given over _____ mins

2nd sample at 8.30am: Exact time ______________ by _______

3rd sample at 9am: Exact time ______________ by _______

4th sample at 10am: Exact time ______________ by _______

5th sample at midday: Exact time ___________ by _______

6th sample at 4pm (before next meropenem dose): Exact time ______________ by _______

A member of the pharmacy team will collect each of the 6 samples from the patient’s room. Do not send to Maidstone.

Any queries contact ...
Appendix 7. Pharmacy staff standard operating procedures for clinical study

Contact Bristol

Serum drug concentrations are being measure by the lab at Southmead Hospital in Bristol. We need to contact them the morning before samples are due to arrive, so they have time to get things ready.

Telephone: 0117 323 5653. Ask for the scientist on assays

Address

Regional Antimicrobial Assay Laboratory
Department of Microbiology
Southmead Hospital
Westbury on Trym
Bristol BS10 5NB

Contact TNT

On the day that samples are due to be collected, phone TNT 0800 100600 in the morning to arrange collection from the Pharmacy between 4.30pm and 5.30pm. Please make it clear that the package will NOT be ready before 4.30pm and that we will be closed after 5.30pm

Record the reference number given to you and the name of the person you are speaking to. This info only needs to be retained until you know the parcel has arrived in Bristol.

Account Number 0630106789

Enter research participants on PAS

NB If you do not have access to PAS, you can email Sarah Dawe instead, quoting patient name, hospital number, date of birth and study number: (MS) 03/44

There is now a field on PAS for you to record that your patient has been recruited to your research project. The only information you need to give is the ethics number of your project.

You can access the PAS field in this way:

On the initial PAS menu, select the function UMD
In ‘User field 1’ enter the LREC number.

It is essential that this information is recorded as soon as a patient is recruited – either by yourself or by a delegated person.

Patient confidentiality will not be breached.

Prepare stickers

Hopefully you will be there to collect blood samples as they are taken. If not, on the day before prepare six stickers ready for blood tubes for the nursing staff. Use the blanks in this file. Information needed – patient name, hospital number, drug for assay, time sample taken (leave blank) and date. Take these to the nurse together with 6 of the brown blood tubes. (Don’t stick the stickers on.)

You will also need to prepare 6 stickers for the plasma tubes (or 12 for colistin), once you have spun them down – same details.
Taking samples – ensuring that they are taken correctly

When the drug is prescribed – check dose times are correct, and endorse chart “Do not change these times”.

On the day before samples are due, ensure the nurse looking after the patient will “handover” to hold off giving the 8am antibiotic dose until you get there just before 8am. Write this information on the dry wipe board in the room too.

On the day of samples, go into the ITU room just before 8am, check that the antibiotic has not been given, then get them to take the first sample.

Go and spin the first sample, but ask the nurse to record the exact time that the antibiotic is given.

Once the first sample has been spun, go back to the room. Check what time the antibiotic was given, and write up on the dry wipe board times for the other samples. If the antibiotic is given exactly at 8am, this would be 8.30am, 9am, 10am, 12pm, then either 2pm (for 6 hourly dosage) or 4pm (8 or 12-hourly dosage).

Return to the patient just before each sample is due to be taken.

Spinning and separating plasma samples.

Use swipe card to get into burns lab. Only pharmacy staff who have received training are allowed to handle bloods (see register in this section). Most of the items you need will be a box on the shelf above the centrifuge.

Samples are unstable in blood, so should be spun and separated as soon as possible.

Put on a pair of gloves before handling any blood tubes, and keep them on for the whole process.

Ensure that the dummy tube in the centrifuge contains approximately the same volume of water as the blood tube you have. If necessary adjust the amount of tap water in the dummy. If you are doing two samples at a time, you will not need to use the dummy.

Place the two tubes in opposite slots in the centrifuge. The tubes need to be pushed right in to be balanced.

Put on the centrifuge lid and spin for 5 minutes at 4500 RPM. (If you need to change the settings, you can do only this if the lid is open.)

Remove the tube from the centrifuge. The easiest way is to take out the outer tube and tip out the serum tube.

Check the tube has separated into the lower layer of red cells and a clear (usually straw coloured) upper plasma layer. If separation is not clear, respin the sample.

Using a pipette, transfer as much of the upper layer as possible into a new tube. (This should be a blank tube. If you run out, ask phlebotomy for more.) Avoid touching the lower layer.

Ensure the new tubes are clearly labelled, including the time the sample was taken.

Check the lids of the new tubes are closed securely.

Discard the old tube and glass pipettes in the yellow sharps bin.

Wrap each new sample tube in Parafilm, then a paper towel, then seal in a plastic bag. Use the small resealable bags from Pharmacy.

Store the new tubes in the bottom of the samples fridge on A Wing Theatre until all samples have been spun down. Ensure that they are put in a bigger bag marked “Antibiotic Study. Do not take these samples to MTW”

For all samples, follow packaging and delivery procedure in this section of the file.
If there are any problems with the centrifuge, first look in the instruction manual kept in the lab. If no help, contact Labtech on 01273 814888. The contact name I have is Anthony Longhurst. As an alternative, you may be able to use the other centrifuge in the Burns Lab – Simon Booth (Charge Nurse on Burns) knows how to operate this.

Packaging and Delivery

- Double check in Pharmacy that TNT has been contacted and that Bristol are aware.
- When all of the samples have been taken* and separated, check all of the tubes have been wrapped in parafilm, then a soft paper towel and put in a sealed plastic bag.
- Place the tubes in one large plastic bag and seal. Put in polystyrene cooler GF3 box with 3 ice packs and covering sheet, ensuring all details are recorded on the sheet.
- Seal box and wrap in brown paper. Use address sticker for Bristol and our address sticker. All these are in the TNT section of the file.
- Complete the Consignment sheet – ensure that you tick it is for next day before 9am delivery.
- On the back of the consignment sheet, there are some stickers with bar codes. Ensure that two of these are stuck to the package.
- Leave package and consignment sheet in Pharmacy for collection. The driver will take the top copy.
- Ensure that someone in dispensary is aware that package should be collected before 5.30pm. If the item has not been collected by then, phone TNT to arrange collection from the Burns Lab. Take the package up to the burns lab and ensure that staff on burns are aware where the package is to be collected. Stick up a pre-printed pink sheet (blanks in this file) in the nurses’ station.

Analysing blood levels

Results should be phoned / faxed through on the day that the samples are received for meropenem and linezolid. Colistin will take longer. If you have not heard by 5pm, please phone them.

Meropenem and Linezolid

- Go into Excel in your PC
- Open Pharmacy General Folder
- Click on “Burns Antibiotic Study”, then “Results”
- Open “Master”
- “Save as” Drug name, number, patient surname, date (see previous entries)
- In “normal” worksheet, amend the times if necessary, and alter the serum concentrations. Do the same in the log sheet.

For meropenem and linezolid, look at the curve – serum concentrations should be above 4mg/L for at least 40% of the dosing interval.

For an eight-hourly dose, they should still be above 4 at three hours 20 minutes.
For a six-hourly dose, should be above 4 at 2½ hours
For a four-hourly, should be above 4 at 1½ hours
For a twelve-hourly dose, should be still above 4 at 4 hour 50 mins

If serum concentrations are below 4mg/L at these times, in most cases it is probably better to advise to increase the dosing frequency rather than increase the dose. You can use the graph to predict what the level if you do increase the frequency or dose.

If a dose change is necessary, ensure the process is repeated at least 24 hours after the dose change.

* For linezolid send the first six samples. The final sample is kept in the fridge overnight and will only be sent the next day if clinically necessary, depending on the results of the first six.
Colistin

Look at the peak level (i.e. after one hour). It should be between 10 and 15 mg / L. If it is not, adjust dose accordingly (rather than frequency).

If the dose is being increased, monitor renal function even more closely and be aware of any signs of neurotoxicity.

If a dose change is necessary, ensure the process is repeated at least 24 hours after the dose change.

Record of pharmacy Staff able to handle blood samples

<table>
<thead>
<tr>
<th>Name</th>
<th>Procedures read and understood (initials)</th>
<th>Hep B status checked</th>
<th>Procedure</th>
<th>Signature</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sharps Policy</td>
<td>Spillage of blood</td>
<td>Sharps injury</td>
<td>Demonstrated by</td>
<td>Supervised by</td>
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</table>
Appendix 8. Patient data collection sheet

The Queen Victoria Hospital NHS

Study: Pharmacokinetics of Antibiotics in Patients with Major Burns

Patient Data Sheet

Antibiotic name: ___________________ Reason for starting antibiotic _____________

Date of sampling: __________________________________________________________

Patient Details

Name ___________________ Hospital Number _________________________

Date of birth ___________________ Male / Female (Please circle)

Weight (last weighed) ________ kg Date last weighed _____________

Height ______________

Burn Details

Date of Burn ___________________ Inhalation Injury? Yes / No

Total burn surface area ______________ %

Full thickness burn surface area __________ % Partial thickness __________ %

Percentage burn remaining on diagnosis of infection ________________ %

Antibiotic Dosing Information for dose when samples taken

Dose number _______ (e.g. if 5 doses had been given before the one being sampled, dose number would be 6).

Exact time of previous dose ___________ Given over ___________ minutes

(ie night dose)

Exact time of dose being tested ___________ Given over ___________ minutes

(ie 8am dose)
Laboratory Investigations on day of sampling.
Please ensure that every effort is made for these to be made on day of sampling. If this has not been possible, record data for the nearest day to this and record date.

Serum creatinine ______________ μmol/L Date measured ______________________

Creatinine clearance __________ mL/min Date measured ______________________

Serum albumin _______________ g/L Date measured ______________________

Antibiotic record of current course (include data after sampling)

<table>
<thead>
<tr>
<th>Date*</th>
<th>Dose</th>
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</table>

Date stopped: Total number of doses:

* If dose changed record details on new row in table

Other antibiotics given during the course

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Date started</th>
<th>Date stopped</th>
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</tbody>
</table>
Microbiology

Date infection diagnosed _____________________
Site of infection if known _____________________

<table>
<thead>
<tr>
<th>Pathogens identified</th>
<th>Date sample taken</th>
<th>Site</th>
<th>Sensitivities</th>
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</table>

Report any adverse events occurring during course of treatment:

__________________________________________________________________________
__________________________________________________________________________
__________________________________________________________________________

All SUSARs must be reported to the Queen Victoria Hospital immediately

Follow-up

Length of stay in ITU ________________________ days     Survived? Yes / No

Date discharged / died ________________________
Appendix 9. Predicted effect of different dose schedules for meropenem

Glossary of abbreviations

Cl Total body clearance (L/hr)
(Cpfd)max Maximum serum concentration following the first dose
(Cpfd)min Minimum serum concentration following the first dose
(Cps)max Maximum steady-state concentration at steady-state (mg/L)
(Cps)min Minimum steady-state concentration at steady-state (mg/L)
Cps Steady state serum concentration for continuous infusion (mg/L)
D Dose (mg)
f Unbound fraction of the drug
IR Infusion rate (mg/hr)
K Elimination rate constant (hr⁻¹)
MIC Minimum inhibitory concentration (mg/L)
T Dose interval (hr)
T > MIC Percentage of the dose interval above the selected MIC
\( t_{\text{inf}} \) Infusion time (hr)
\( T_{\text{to} \rightarrow \text{MIC}} \) The time from the start of the infusion to reach the MIC (hr)
\( T_{\text{to} < \text{MIC}} \) The time from the end of the infusion to drop back below the MIC (hr)
Vd Volume of distribution as calculated in the β-phase of the elimination slope (L)

Bolus Dosing (1)

Maximum serum concentration following the first dose (Equation 1.1)

\[(Cp_{\text{fd}})_{\text{max}} = \frac{D}{Vd}\]

Maximum steady-state concentration (Equation 1.2)

\[(Cp_{\text{ss}})_{\text{max}} = \frac{(Cp)0}{1 - e^{-K\tau}}\]

Minimum or “trough” serum concentration at steady-state (Equation 1.3)

\[(Cp_{\text{ss}})_{\text{min}} = (Cp_{\text{ss}})_{\text{max}} \times e^{-K\tau}\]

Percentage of the dose interval above the MIC at steady-state (Equation 1.4)

\[T > MIC = ln\left(\frac{\text{Dose} \times f}{V \times \text{MIC}}\right) \times \frac{Vd}{Cl} \times \frac{100}{\tau}\]
Intermittent infusion (2)

Intermittent infusion following first dose

Peak concentration at the end of the infusion (Equation 2.1)

\[ (C_{pd})_{max} = \frac{IR}{Cl} (1 - e^{-Kt_{inf}}) \]

Minimum (Trough) concentration (Equation 2.2)

\[ (C_{pd})_{min} = (C_{pd})_{max} e^{-Kt} \]

Time from the start of the infusion to reach the MIC (Equation 2.3)

\[ T_{to > MIC} = \frac{\ln(1 - (MIC \times Cl \div IR))}{-K} \]

Time from the end of the infusion to drop back below the MIC (if \( (C_{pd})_{min} \) is less than the MIC) (Equation 2.4)

\[ T_{to < MIC} = \frac{\ln(MIC \div (C_{pd})_{max})}{-K} \]

Percentage of the first dose above the MIC, \( T > MIC \) (Equation 2.5)

\[ T > MIC = \frac{100 (\tau - t_{to > MIC} - (\tau - (t_{mf} + t_{to < MIC})))}{\tau} \]
**Intermittent infusion at steady-state**

The peak concentration at the end of the infusion (assuming that distribution is complete by the end of the infusion) (Equation 2.6)

\[
(Cp_{ss})_{max} = \frac{IR}{Cl} \times \frac{(1 - e^{Kt_{inf}})}{(1 - e^{-Kt}})
\]

The trough concentration (Equation 2.7)

\[
(Cp_{ss})_{min} = (Cp_{ss})_{max}e^{-Kt_{inf}}
\]

For patients who have a trough level below the MIC, the predicted time from the start of each infusion to reaching the MIC (Equation 2.8)

\[
T_{to>MIC} = \ln\left(\frac{1 - (MIC - (Cp_{ss})_{min}) \times Cl \div IR}{-K}\right)
\]

For patients who have a trough level below the MIC, the predicted time from the end of the infusion that the concentration will drop back below the MIC (Equation 2.9)

\[
T_{to<MIC} = \frac{ln(MIC \div (Cp_{ss})_{max})}{-K}
\]

For patients who have a trough level below the MIC, the percentage of the dose interval above 4mg/L is as for 2.5
Continuous infusion (3)

The predicted steady-state serum concentration (Equation 3.1)

\[ Cp_{ss} = \frac{IR}{Cl} \]

The time from the start of the infusion to reach the MIC is as for 2.3.

Reference

Appendix 10. Protocol for clinical study

Protocol

Pharmacokinetics of Antibiotics in Adults with Major Burns

Version 2, 9th July 2003

Principal Investigator

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Queen Victoria Hospital NHS Trust, East Grinstead

Co-Investigators

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Queen Victoria Hospital NHS Trust, East Grinstead

Dr B. Stewart, Consultant Microbiologist
Surrey and Sussex NHS Trust

Dr E.L. Teare, Consultant Microbiologist
Chelmsford Public Health Laboratory Service

Collaborators

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Dr S. E. James, Senior Scientist, Wound Healing Group
Blond McIndoe Centre, Queen Victoria Hospital NHS Trust

Professor A.W. Lloyd, Professor of Biomedical Materials
School of Pharmacy and Biomolecular Science, University of Brighton

Dr G. Standen, Research Technician in Chemistry
School of Pharmacy and Biomolecular Science, University of Brighton
Summary

Patients with major burns experience pathological changes which have been shown to influence the pharmacokinetics of antibiotics. Subsequently it has been demonstrated that conventional doses of some antibiotics given to patients with major burns may result in sub-therapeutic serum concentrations. This multi-centred study aims to measure serum concentrations of four antibiotics – colistin, meropenem, imipenem and linezolid. These antibiotics are used to treat life-threatening infections in burns patients, but there is little pharmacokinetic data known in this population. The results will be fed back to participating burns units to adjust doses if necessary, and the pharmacokinetic data obtained used to develop a model for the dosing of these antibiotics in this group of patients. These results will be combined with previous pharmacokinetic studies for a meta-analysis to further develop a model for dosing of antibiotics in major burns patients.

Introduction

Severe burn injury requires hospitalisation and may be life-threatening. A burn does not only damage the skin, but affects many organs throughout the body, resulting in complex pathological changes (Bonate 1990). When a major burn first occurs there is fluid and plasma protein loss from the vascular system, as a result of loss of capillary integrity. This causes a drop in cardiac output and tissue hypoperfusion. To prevent shock occurring, large volumes of intravenous fluids are required for adults with a total burn surface area of at least 15%. This acute phase lasts about 48 hours, after which a hypermetabolic phase occurs, which can last several weeks. This is characterised by an increase in both core temperature and cardiac output.

Infection is a major cause of morbidity and mortality in patients with severe burns, who survive the initial burn (Moore 1984, Reig 1994, Bang 2000) and it has been estimated that as many as 75 per cent off all deaths following burn injuries are related to infection (Polk 1979). Acinetobacter, in particular, is a problem in burns patients, as it is an opportunistic pathogen that frequently exhibits resistance to multiple antibiotics (Bergogone-Berezin 1995). Another emerging pathogen is vancomycin-resistant enterococci. Clinical manifestations of VRE in patients with severe burns may include septicaemia, pneumonia and wound infections (McManus 1998).

For an antibiotic to be an effective treatment for bacterial infections there must be a sufficient concentration of drug at the site of the infection for an adequate length of time. For example, in an animal study, Walker et al (1994) found that meropenem concentrations needed to be above the minimum inhibitory concentration (MIC) for approximately 33 – 40% of the dosing interval to produce a bacteriostatic effect. In most cases, recommended doses of antibiotics will achieve this,
but in patients with major burns standard doses may not be sufficient. The pathological changes that occur may result in major shifts of fluid volumes, so increasing the volume of distribution and decreasing the concentration of the drug. Additionally the greater renal blood flow due to the change in cardiac output may cause an increase in clearance and a shorter elimination half-life. Previous studies have shown a need for increased doses of some antibiotics (Zaske 1976, Garrelts 1988 & 1996, Rybak 1990, Bourget 1996, Lesne Hulin 1997 &1999).

Although Acinetobacter is a major pathogen in burns, there is little published literature on the pharmacokinetics of the drugs used to treat infections caused by it. In the Queen Victoria Hospital Burns Centre Acinetobacter spp are usually only sensitive to carbapenems (meropenem or imipenem), amikacin, and sometimes only to colistin. A similar pattern has been reported in other units in the UK (personal communications).

Of these antibiotics, amikacin is the most widely studied in burns patients. Results indicate that there is an increased dose requirement to attain therapeutic serum concentrations (Zaske 1978, Kopcha 1991). As amikacin levels are routinely measured in hospitals, it is easy to adjust doses accordingly. This facility is generally not available for imipenem, meropenem or colistin. Pharmacokinetic data on the carbapenems in burn patients are very limited (Boucher 1990, Yoshida 1993 and Weinbren 1999), but indicate that higher than standard doses may be required in some patients. There have been no studies on colistin in burns patients.

Vancomycin-resistant enterococci (VRE) can be treated by either linezolid or quinupristin with dalfopristin (Synercid®). There is one report of linezolid being used successfully to treat VRE septicaemia in two burns patients (Atkins 2002). However, it has been shown that enterococcal resistance to linezolid may be caused by prolonged courses and / or subtherapeutic dosing, complex concurrent disease and non-removal of infected prosthetic devices (Zurenko 1999). There are no pharmacokinetic studies of linezolid in burns patients and because pharmacokinetic parameters may be altered, it is possible that standard doses of linezolid may result in subtherapeutic serum levels and the development of resistance. When quinupristin with dalfopristin was used to treat VRE in a patient with major burns, resistance to the combination was seen after a week of treatment (Rose 2002). This could have been because therapeutic serum concentrations were not achieved. There are no pharmacokinetic studies of these antibiotics in burns patients, but as linezolid is the drug of choice for treatment of VRE at the Queen Victoria Hospital, quinupristin and dalfopristin are not included in this study.
Aims and Objectives of the Study

Aims of the Study

The principal aims of the study are:
To investigate the pharmacokinetic parameters of four antibiotics when administered to patients with major burns
To produce dosing guidelines for the use of these antibiotics.

Study Objectives
To measure the serum concentrations of imipenem, meropenem, colistin and linezolid in adults with major burns (>15% total body surface area) receiving these antibiotics for treatment of severe infections.
To compare the serum concentrations with those required to treat likely infections.
To calculate pharmacokinetic parameters such as volume of distribution, clearance and elimination half-life.
To investigate the influence of patient factors on the serum concentrations and pharmacokinetic parameters.
To produce dosage guidelines for the use of these antibiotics in adults with major burns.
To ascertain, using the data generated by the study and that previously published, whether there is a model for the dosing of all antibiotics in burns patients.
Plan of Study

Location
The study will be conducted initially on patients at the Queen Victoria Hospital, East Grinstead and Broomfield Hospital (Mid Essex Hospital Services NHS Trust), but extended to include other burns centres in the UK. For this reason an application will be made for Multi-Centre Research Ethics Committee approval. It is anticipated that the period of data collection will be three years.

Patient Recruitment
Suitable patients will be identified by the consultant microbiologist, as the antibiotics included in the study will only be commenced on microbiological advice. Before the patient is approached, agreement will be confirmed with the consultant burns surgeon.

A minimum of twelve patients for each antibiotic will be recruited. It is envisaged that this will take approximately three years.

Inclusion Criteria
Adults with major burns (>15% total body surface area) and infection requiring the use of any of the following antibiotics: imipenem, meropenem, colistin or linezolid. The decision to use these antibiotics will be that of the patient’s clinician and will be determined by the infection type and microbiological testing.

Exclusion criteria
Patients under the age of sixteen years, pregnancy and lactation. Patients with known or suspected blood-borne viruses.

Consent
Where possible, consent will be obtained from the patient. In most cases, the patient will be unable to give consent due to sedation. This will be assessed by the patient’s clinician. Under such conditions, if there is a known next-of-kin, s/he will be asked if, in his/her opinion, the patient would not object to inclusion in the study. The study will be explained to the patient (or next-of-kin) and a patient information sheet given. After at least 24 hours, consent / agreement will asked for. If there is a positive response, forms will then be completed. Retrospective consent will be sought from all surviving patients when no longer sedated.

If the patient is unable to communicate in English, local arrangements will be made for a translator.
**Data Collection**

The following will be recorded for all individuals recruited into the study:

1. **Patient Demographics**
   - Age and gender
   - Weight

2. **Burn Details**
   - Burn total body surface area
   - Full and partial thickness burn surface area
   - Presence of inhalation injury
   - Percentage burn remaining at time of diagnosis of infection
   - When patient last grafted

3. **Details of infection**
   - Date infection diagnosed
   - Site of infection the antibiotic is being used to treat if known and date
   - Any identified pathogens and date
   - Sensitivities (on day of starting antibiotics)

4. **Routine laboratory investigations (on day 1 or 2 of antibiotic treatment)**
   - Serum creatinine and creatinine clearance
   - Serum albumin
   - Cardiac output and method of measurement

5. **Other**
   - Day since burn when blood taken

In addition the following outcome data will be collected:

- time to no microbiological growth of the organisms the antibiotics have been used to treat
- length of stay in ITU
- survival / mortality.

**Doses**

Antibiotics will be administered at the dose decided by the patient's clinician. These will be based on the Summaries of Product Characteristics produced by the manufacturers of each antibiotic.

**Sampling details**

Serial blood samples will be taken, once the patient has achieved steady state (at least 24 hours after treatment started) in order to establish the plasma concentration profile of the
antibiotic. For each series, six 3ml samples will be needed over one dosing interval (usually 8 hours). This number is needed to measure the percentage of time that the concentration is above the minimum inhibitory concentration. If a patient is on more than one antibiotic, samples should be taken over different dosing intervals.

If samples are due to be taken when the patient is to undergo surgery where there is likely to be a significant amount of bleeding, samples should not be taken until the following day.

Blood will be taken from an arterial line which has already been assigned for blood sampling (irrespective of the study) and will cause no discomfort. To protect against needle stick injury, blood spillage, infection and air embolism, a closed, needle-free, self-sealing, access system is used.

Samples will be taken immediately before the dose is given (to ensure that steady-state has been reached) then:
Meropenem, colistin and imipenem (i.e. 8 hourly intervals) at 30 minutes, 1 hour, two hours, four hours and eight hours after the dose.
Imipenem can sometimes be given every six hours. If this should occur, the final sample will be taken immediately before the next dose is due (six hours).
For linezolid which is given every 12 hours, samples will be taken at 1 hour, 2 hours, 4 hours, 8 hours and 12 hours.

_Determination of serum concentrations_
Serum concentrations will be determined by validated methods of HPLC analysis at either at the University of Brighton (colistin) or Southmead Hospital in Bristol (linezolid, imipenem and meropenem).

_Feedback_
The patient’s clinician will be informed of the serum concentrations measured. This will usually be on the next working day. If, based on these results, the clinician considers a dose change is required, another series of six 3ml samples can be taken once steady-state is achieved. This process can continue as long as the clinician thinks necessary. If there is any significant change in renal function (> 20% change in creatinine or creatinine clearance), another series of samples can be requested to ensure efficacy or prevent toxicity.
Analysis of Results
The results obtained will be subjected to appropriate pharmacokinetic, mathematical and statistical analysis. Data will be compared with previous studies in healthy volunteers, and for any correlation with other data collected such as age, renal function and size of burn. This will take place after twelve patients have been recruited. At this stage it may be possible to recommend a different dose in burns patients, or establish that no dose change is necessary. If this is not possible, it should be clear whether there is a significant risk of underdosing. If the latter should apply, it may be necessary to recruit more patients to the study, or recommend that in the future all burns patients receiving these antibiotics should have therapeutic drug level monitoring.

Finance
This study has obtained financial donations from Pharmacia and Forest Laboratories to cover costs of transport and analysis. Meropenem levels are already provided free-of-charge by AstraZeneca. The appropriate pharmaceutical companies have offered materialistic support to the study.

This study is supported by the British Society of Antimicrobial Chemotherapy, Burns Working Party.

References


Zaske DE, Sawchuk RJ Gerding DN, Strate RG (1976) Increased dosage requirements of gentamicin in burns patients. *J Trauma* 16: 824 – 8


Appendix 11. Research subject information sheets and consent forms

The Queen Victoria Hospital NHS

NHS Trust

Research Subject Information Sheet, Version 2, 9th July 2003

Pharmacokinetics of Antibiotics in Adults with Major Burns

You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this.

What is the purpose of the study?
We are studying ways of improving the use of the antibiotics that we give to patients in the burns units in the UK. Infections are a common problem for patients with large burns, as the damaged skin finds it hard to prevent bacteria getting into the body. To fight this, we give powerful antibiotic injections.

Each antibiotic you are given has a recommended dose. This dose is based on studies on people without burns. There has now been some work to make us think that if you have a large burn, you may need bigger doses than usual. This may be because you have more fluid in your body than usual, so diluting the antibiotics. It could also be because your kidneys are working overtime, and you are losing antibiotic faster than normal. (The usual way the body gets rid of antibiotics is through the kidneys and out in the urine.)

We plan to take blood samples from patients who have been prescribed any of four antibiotics by their doctor. We hope to include twelve patients for each antibiotic. This study does not involve patients receiving any untried drugs. The doctors choose the antibiotic(s), because they think it is the best treatment. We will then measure the amount of antibiotic in each blood sample and give the results back to the doctor. He or she may then decide that is necessary to change the dose. If there is a dose change, we will repeat the blood tests, to check the new dose. The blood tests may need to be repeated after any dose change the doctor feels it is necessary to make. After three years, we will look at the results from all patients, to see if we should recommend a different starting dose for future patients with major burns.

Why have I been chosen?
You have been chosen because you have an infection and your doctor thinks it is necessary to give you one or more of the antibiotics chosen for the study.

The antibiotic(s) we would like to measure from you is/are called:

..........................................................................................................................................................

Antibiotics are given until the doctor thinks they are either no longer necessary or appropriate. This is usually for one to two weeks.
Do I have to take part?
It is up to you whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What will happen to me if I take part?
In order to find out how much antibiotic you have in your body, we will need to take six blood samples of 3ml each. In total, this will be just more than a tablespoonful. This will usually be on the day after you have started the antibiotic. We will also record information about you such as your age and the size of your burn to see if this relates to the blood concentrations we measure. This information will be kept confidential.

When we get the results of the blood test, we will tell the doctor looking after you. He or she may then decide that your dose should be changed. If this happens, we would like to take another six blood samples, to check whether the new dose is better for you. This process may be repeated any time the doctor thinks your dose may need to be changed whilst you are receiving the antibiotic. You will probably receive the antibiotic for one to two weeks.

What do I have to do?
Nothing. This study should not cause any inconvenience to you. A doctor or nurse will take the blood from you. This does not mean inserting a needle into a vein each time, as you already have a “line” (small tube into the vein) that we use to take your blood for other tests. You will not feel anything when the blood is taken.

What are the drugs being tested?
The four antibiotics are called colistin, imipenem, meropenem and linezolid. They have all been used for several years and are not experimental drugs.

What are the alternatives for treatment?
Depending on the type of infection you have, there may or may not be any other drugs that can be used. You are receiving the antibiotic that the doctor thinks is the best treatment for you.

What are the side-effects of any treatment received when taking part.
All medication can cause side-effects. Your doctor can explain the possible side-effects of the antibiotic you will receive and give you the patient information leaflet produced by the drug company.

What are the possible disadvantages and risks of taking part.
There are unlikely to be any disadvantages. There is always a very small risk of infection occurring when blood is taken, or an air bubble getting into the blood stream. You already have a system in place to protect against this for when we take blood for other reasons. The blood taken is a small amount. If at any stage you need to be given blood, it is likely to be due to other blood loss.

What are the possible benefits of taking part?
The information we get will be good for you, as it will help make sure that you get the best dose of antibiotic. Patients in the future who need antibiotics may also benefit. We will look at the data from everyone who takes part in the study, and see if we should recommend a different starting dose.

What if new information becomes available?
Sometimes during the course of treatment, new information becomes available about the antibiotics being studied. This is unlikely to occur with this study, as you will probably only receive the antibiotic for a week or two. If it does happen, your doctor will tell you about it and discuss with
you whether you want to continue with study. If you decide to continue in the study, you will be asked to sign an updated consent form.

Also, on receiving new information your doctor might consider it to be in your best interests to withdraw you from the study. He/she will explain the reasons and arrange for your care to be continued.

**What happens when the research study stops?**
As you are only receiving a short course of antibiotics, you will not be affected by the study stopping.

**What if something goes wrong?**
If you have any side-effects from the antibiotics you receive, the doctor will discuss with you whether it would be best for you to stop treatment, or be given other drugs to treat side-effects.

If you have a complaint, you can either speak to staff looking after you, or ask to speak to (or write to) the Hospital Patient Liaison and Complaints Manager.

**Will my taking part in this study be kept confidential?**
All information which is collected about you during the course of the research will be kept strictly confidential. Blood tubes sent to the laboratories will have your name, date of birth and hospital number on for identification purposes. All other information which leaves the hospital will have your name and address removed so that you cannot be recognised from it.

**What will happen to the results of the study research?**
Once the data is analysed we plan to publish the results in one of the medical journals. This is likely to be 2007. You will not be identified in any report or publication. If you would like a copy of the results, please let us know.

**Who is organising and funding the research?**
The research is being organised by Jane Allen, Chief Pharmacist at the Queen Victoria Hospital in East Grinstead, in conjunction with the University of Brighton.

Your doctor is not being paid for including you in this study. Transport and the laboratory costs are being paid for by educational grants from the pharmaceutical companies, Pharmacia (who make linezolid), Forest laboratories (who make colistin) and AstraZeneca (who make meropenem).

**Who has reviewed the study?**
The study has been reviewed and approved by the (COREC) and (Local) Research Ethics Committees

Contact for Further Information
For further information, please contact:

Jane Allen
Chief Pharmacist
Queen Victoria Hospital
East Grinstead
West Sussex RH19 3DZ

Tel 01342 414214
Email: jane.allen@qvh.nhs.uk

Thank you for reading this leaflet. If you decide to take part in the study, thank you! You will be given a copy of this information sheet and a signed consent form to keep.
CONSENT FORM

Pharmacokinetics of Antibiotics in Adults with Major Burns

Name of Researcher:

I confirm that I have read and understand the information sheet dated 9th July 2003 (version 2) for the above study and have had the opportunity to ask questions.

I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

I understand that sections of any of my medical notes may be looked at by responsible individuals from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.

I agree to take part in the above study.

Name of Patient: ____________________________ Date: _______________ Signature: _________________

Name of Person taking consent (if different from researcher): ____________________________ Date: _______________ Signature: _________________

Researcher: ____________________________ Date: _______________ Signature: _________________

1 for patient; 1 for researcher; 1 to be kept with hospital notes
Relative / Next-of-kin information sheet, Version 2, 9th July 2003

Pharmacokinetics of Antibiotics in Adults with Major Burns

You are being invited to agree for your relative or next-of-kin to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this.

What is the purpose of the study?
We are studying ways of improving the use of the antibiotics that we give to patients in the burns units in the UK. Infections are a common problem for patients with large burns, as the damaged skin finds it hard to prevent bacteria getting into the body. To fight this, we give powerful antibiotic injections.

Each antibiotic a patient is given has a recommended dose. This dose is based on studies on people without burns. There has now been some work to make us think that if patients have large burns, they may need bigger doses than usual. This may be because they have more fluid in your body than usual, so diluting the antibiotics. It could also be because their kidneys are working overtime, and they are losing antibiotic faster than normal. (The usual way the body gets rid of antibiotics is through the kidneys and out in the urine.)

We plan to take blood samples from patients who have been prescribed any of four antibiotics by their doctor. We plan to include twelve patients for each antibiotic. This study does not involve patients receiving any untried drugs. The doctors choose the antibiotic(s), because they think it is the best treatment. We will then measure the amount of antibiotic in each blood sample and give the results back to the doctor. He or she may then decide that is necessary to change the dose. If there is a dose change, we will repeat the blood tests, to check the new dose. The blood tests may need to be repeated after any dose change the doctor feels it is necessary to make. After three years, we will look at the results from all patients, to see if we should recommend a different starting dose for future patients with major burns.

Why has my relative been chosen?
He or she has been chosen because s/he has an infection and the doctor thinks it is necessary to give him or her one or more of the antibiotics chosen for the study.

The antibiotic(s) we would like to measure is/are called:

........................................................................................................................................................................

Antibiotics are given until the doctor thinks they are either no longer necessary or appropriate. This is usually for one to two weeks.

Does my relative have to take part?
As your relative is unable to give consent at the moment, we would like to get your agreement. If you do agree for him or her to take part you will be given this information sheet to keep and be asked to sign a form to show your agreement. If you agree to the study, you are still free to ask to stop the study at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care the patient receives.
When the patient is well enough to give consent, we will explain the study and ask for his or her permission to use the information we have already taken. If s/he is not in agreement we will not use the data for our analysis after three years.

**What will happen to the patient if he/she takes part?**
In order to find out how much antibiotic there is in the patient’s body, we will need to take six blood samples of 3ml each. In total, this will be just more than a tablespoonful. This will usually be on the day after starting the antibiotic. We will also record information about the patient such as age and the size of burn to see if this relates to the blood concentrations we measure. This information will be kept confidential.

When we get the results of the blood test, we will tell the doctor looking after the patient. He or she may then decide that the dose of antibiotic should be changed. If this happens, we would like to take another six blood samples, to check whether the new dose is better. This process may be repeated any time the doctor thinks the dose may need to be changed whilst the patient is receiving the antibiotic. The antibiotic will probably be given for one to two weeks.

**What does the patient have to do?**
Nothing. This study should not cause any inconvenience to the patient. A doctor or nurse will take the blood. This does not mean inserting a needle into a vein each time, as the patient already has a “line” (small tube into the vein) that we use to take blood for other tests. S/he will not feel anything when the blood is taken.

**What are the drugs being tested?**
The four antibiotics are called colistin, imipenem, meropenem and linezolid. They have all been used for several years and are not experimental drugs.

**What are the alternatives for treatment?**
Depending on the type of infection, there may or may not be any other drugs that can be used. The patient is receiving the antibiotic that the doctor thinks is the best treatment for him/her.

What are the side-effects of any treatment received when taking part. All medication can cause side-effects. The doctor can explain the possible side-effects of the antibiotic and give you the patient information leaflet produced by the drug company.

**What are the possible disadvantages and risks of taking part?**
There are unlikely to be any disadvantages. There is always a very small risk of infection occurring when blood is taken, or an air bubble getting into the blood stream. You already have a system in place to protect against this for when we take blood for other reasons. The blood taken is a small amount. If at any stage the patient needs to be given blood, it is likely to be due to other blood loss.

**What are the possible benefits of taking part?**
The information we get will be good for the patient, as it will help make sure that s/he gets the best dose of antibiotic. Patients in the future who need antibiotics may also benefit. We will look at the data from everyone who takes part in the study, and see if we should recommend a different starting dose.

**What if new information becomes available?**
Sometimes during the course of treatment, new information becomes available about the antibiotics being studied. This is unlikely to occur with this study, as the patient will probably only receive the antibiotic for a week or two. If it does happen, the doctor will tell you about it and discuss with you whether you want your relative to continue with study. If you decide to continue, you will be asked to sign an updated agreement form.

Also, on receiving new information your doctor might consider it to be in the patient’s best interests to be withdrawn from the study. He/she will explain the reasons and arrange for his/her care to be continued.
What happens when the research study stops?
As the patient is only receiving a short course of antibiotics, s/he will not be affected by the study stopping.

What if something goes wrong?
If the patient has any side-effects from the antibiotics, the doctor will discuss with you whether it would be best to stop treatment, or to prescribe other drugs to treat side-effects.

If you have a complaint, you can either speak to staff looking after the patient, or ask to speak to (or write to) the Hospital Patient Liaison and Complaints Manager.

Will the patient taking part in this study be kept confidential?
All information which is collected about the patient during the course of the research will be kept strictly confidential. Blood tubes sent to the laboratories will have his/her name, date of birth and hospital number on for identification purposes. All other information which leaves the hospital will have his/her name and address removed so that s/he cannot be recognised from it.

What will happen to the results of the study research?
Once the data is analysed we plan to publish the results in one of the medical journals. This is likely to be 2007. The patient will not be identified in any report or publication. If you would like a copy of the results, please let us know.

Who is organising and funding the research?
The research is being organised by Jane Allen, Chief Pharmacist at the Queen Victoria Hospital in East Grinstead, in conjunction with the University of Brighton.

The doctor is not being paid for including the patient in this study. Transport and the laboratory costs are being paid for by educational grants from the pharmaceutical companies, Pharmacia (who make linezolid), Forest Laboratories (who make colistin) and AstraZeneca (who make meropenem).

Who has reviewed the study?
The study has been reviewed and approved by the (COREC) and (Local) Research Ethics Committees

Contact for Further Information
For further information, please contact:

Jane Allen
Chief Pharmacist
Queen Victoria Hospital
East Grinstead
West Sussex RH19 3DZ

Tel 01342 414214
Email: jane.allen@qvh.nhs.uk

Thank you for reading this leaflet. If you decide to allow the patient to join the study, thank you! You will be given a copy of this information sheet and a signed agreement form to keep.
Next-of-Kin Agreement Form Version 2, 9th July 2003

Centre Number: 01
Study Number: (MS) 03/44 MREC 3/3/45
Patient Identification Number for this trial:

NEXT-OF-KIN AGREEMENT FORM

Pharmacokinetics of Antibiotics in Adults with Major Burns

Name of Researcher:

Please initial box

1. I confirm that I have read and understand the information sheet dated 9th July 2003 (version 2) for the above study and have had the opportunity to ask questions.

2. I understand that my agreement to the study is voluntary and that I am free to stop the study at any time, without giving any reason, without the patient's medical care or legal rights being affected.

3. I understand that sections of any of the medical notes may be looked at by responsible individuals from regulatory authorities where it is relevant to the patient taking part in research. I agree for these individuals to have access to my records.

4. In my opinion the patient would not object to taking part in the study.

_________________________
Name of Patient

_________________________  ____________________
Name of Next-of-Kin  Date  Signature

_________________________  ____________________
Name of Person taking consent  Date  Signature
(if different from researcher)

_________________________  ____________________
Researcher  Date  Signature

1 for next-of-kin; 1 for researcher; 1 to be kept with hospital notes
Pharmacokinetics of Antibiotics in Adults with Major Burns

When you were on the ventilator or sedated, we took the decision to include you in a research study. This is because we were unable to ask for your consent, but felt it was in your best interests to be included. If you have a next-of-kin, we will have explained the study to him or her, and obtained his/her agreement for you to take part in the study until now, when you are well enough for you to decide for yourself.

We are now asking for your permission to use the data we have taken. Before you decide, it is important for you to understand why the research is being done and what it involves. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to give your consent.

Thank you for reading this.

What is the purpose of the study?
We are studying ways of improving the use of the antibiotics that we give to patients in the burns units in the UK. Infections are a common problem for patients with large burns, as the damaged skin finds it hard to prevent bacteria getting into the body. To fight this, we give powerful antibiotic injections.

Each antibiotic you were given has a recommended dose. This dose is based on studies on people without burns. There has now been some work to make us think that if you have a large burn, you may need bigger doses than usual. This may be because you have more fluid in your body than usual, so diluting the antibiotics. It could also be because your kidneys are working overtime, and you are losing antibiotic faster than normal. (The usual way the body gets rid of antibiotics is through the kidneys and out in the urine.)

The study involves taking blood samples from patients who have been prescribed any of four antibiotics by their doctor. We hope to include twelve patients for each antibiotic. It does not involve patients receiving any untried drugs. The doctors choose the antibiotic(s), because they think it is the best treatment. We then measure the amount of antibiotic in each blood sample and give the results back to the doctor. He or she may then decide that is necessary to change the dose. If there is a dose change, we repeat the blood tests, to check the new dose. The blood tests may need to be repeated after any dose change the doctor feels it is necessary to make. After three years, we will look at the results from all patients, to see if we should recommend a different starting dose for future patients with major burns.

Why was I chosen?
You were chosen because you had an infection and your doctor thought it is necessary to give you one or more of the antibiotics chosen for the study.

The antibiotic(s) we measured from you was/were called:

…………………………………………………………………………………………………

Antibiotics are given until the doctor thinks they are either no longer necessary or appropriate. This is usually for one to two weeks. We can tell you how long yours were given for.
Do I have to give my consent?
It is up to you if you want to give your consent now. If you agree, you will be given this information sheet to keep and be asked to sign a consent form. If you are not happy to give consent, we will not use any of the information we have collected about you.

What has happened to me so far?
In order to find out how much antibiotic you had in your body, we took six blood samples of 3ml each. In total, this is just more than a tablespoonful. This was probably on the day after you started the antibiotic. We also recorded information about you such as your age and the size of your burn to see if this related to the blood concentrations we measured. This information is kept confidential.

When we got the results of the blood test, we told the doctor looking after you. He or she may have then decided that your dose should be changed. If this happened, we may have taken another six blood samples, to check whether the new dose was better for you. This process may have been repeated any time the doctor thought your dose may have needed to be changed whilst you were receiving the antibiotic. You probably received the antibiotic for one to two weeks. Your doctor can tell you how many sets of blood were taken and whether any dose changes were made as a result of the blood measurements.

What did I have to do?
Nothing. This study should not have caused any inconvenience to you. A doctor or nurse took the blood from you. This did not mean inserting a needle into a vein each time, as you already had a “line” (small tube into the vein) that we used to take your blood for other tests. You did not feel anything when the blood was taken.

What are the drugs being tested?
The four antibiotics are called colistin, imipenem, meropenem and linezolid. They have all been used for several years and are not experimental drugs.

What were the alternatives for treatment?
Depending on the type of infection you had, there may or may not have been any other drugs that could be used. You received the antibiotic that the doctor thought was the best treatment for you.

What were the side-effects of any treatment received when taking part.
All medication can cause side-effects. Your doctor can explain the possible side-effects of the antibiotic you received and give you the patient information leaflet produced by the drug company.

What are the possible disadvantages and risks of taking part?
There were unlikely to be any disadvantages. There is always a very small risk of infection occurring when blood is taken, or an air bubble getting into the blood stream. You already have a system in place to protect against this for when we take blood for other reasons. The blood taken was small amount. If at any stage you needed to be given blood, it was likely to be due to other blood loss.

What are the possible benefits of taking part?
The information we got may have been good for you, as it helped make sure that you were given the best dose of antibiotic. Patients in the future who need antibiotics may also benefit. We will look at the data from everyone who takes part in the study, and see if we should recommend a different starting dose.

What if new information becomes available?
Sometimes during the course of treatment, new information becomes available about the antibiotics being studied. This is unlikely to occur with this study, as the antibiotic is probably only given for a week or two. If it did happen, your doctor might have considered for it to be in your best interests to withdraw you from the study. He/she can explain the reasons and tell you how your care was continued.
What happens when the research study stops?
As you only received a short course of antibiotics, you would not have been affected by the study stopping.

What if something went wrong?
If you had any side-effects from the antibiotics you received, the doctor would have decided if it was best for you to stop treatment, or be given other drugs to treat side-effects.

If you have a complaint, you can either speak to staff looking after you, or ask to speak to (or write to) the Hospital Patient Liaison and Complaints Manager.

Will my taking part in this study be kept confidential?
All information which is collected about you during the course of the research will be kept strictly confidential. Blood tubes sent to the laboratories had your name, date of birth and hospital number on for identification purposes. All other information which leaves the hospital will have your name and address removed so that you cannot be recognised from it.

What will happen to the results of the study research?
Once the data is analysed we plan to publish the results in one of the medical journals. This is likely to be 2007. You will not be identified in any report or publication. If you would like a copy of the results, please let us know.

Who is organising and funding the research?
The research is being organised by Jane Allen, Chief Pharmacist at the Queen Victoria Hospital in East Grinstead, in conjunction with the University of Brighton.

Your doctor was not paid for including you in this study. Transport and the laboratory costs were paid for by educational grants from the pharmaceutical companies, Pharmacia (who make linezolid), Forest laboratories (who make colistin) and AstraZeneca (who make meropenem).

Who has reviewed the study?
The study has been reviewed and approved by the (COREC) and (Local) Research Ethics Committees

Contact for Further Information
For further information, please contact:

    Jane Allen
    Chief Pharmacist
    Queen Victoria Hospital
    East Grinstead
    West Sussex RH19 3DZ

    Tel     01342 414214
    Email:  jane.allen@qvh.nhs.uk

Thank you for reading this leaflet. If you decide to take part in the study, thank you! You will be given a copy of this information sheet and a signed consent form to keep.
### Pharmacokinetics of Antibiotics in Adults with Major Burns

#### Ward Procedure and Checklist

<table>
<thead>
<tr>
<th>Step</th>
<th>Completed / checked by</th>
<th>Date / Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification of patient</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suitable patients will be identified by the consultant microbiologist when advising to initiate therapy.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microbiologist’s name</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotics started as usual</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotics should be prescribed at the usual recommended dose. For advice on this see section 5 (turquoise) of this file.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If the antibiotic is prescribed six-hourly, give at 8am, 2pm, 8pm and 2am</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If the antibiotic is prescribed eight-hourly, give at 8am, 4pm and midnight.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If the antibiotic is prescribed twelve-hourly, give at 8am and 8pm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Check patient fits the inclusion / exclusion criteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sixteen years or over</td>
<td></td>
<td></td>
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<tr>
<td>Total body surface area of 15% or greater</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Starting meropenem, linezolid or colistin</td>
<td></td>
<td></td>
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<tr>
<td>Not pregnant or breast-feeding</td>
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<td></td>
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<tr>
<td>No known or suspected blood-borne viruses e.g. HIV or hepatitis B</td>
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<td></td>
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<tr>
<td>Obtain agreement from consultant burns surgeon</td>
<td></td>
<td></td>
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<tr>
<td>Name</td>
<td>Signature</td>
<td></td>
</tr>
<tr>
<td>(Can be obtained verbally and signed later)</td>
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<td></td>
</tr>
<tr>
<td>Inform Pharmacist if not already aware</td>
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<tr>
<td>bleep 247 or 215, or Ext 4214.</td>
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</tr>
<tr>
<td>If out of hours, phone Jane Allen on mobile 07988 556538 or via QVH switchboard.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If receiving i.v. colistin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacy need to contact Bristol to check that have staff to perform assay. (More labour intensive than other assays.)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Discuss with patient or next-of-kin & give out information sheet
Information sheets are available to explain the study. These should be given out and discussed at least 24 hours before consent is requested. At no stage should patients or next-of-kin feel any pressure to take part in the study. It should be made very clear that the same drugs will be given whether or not they take part.

There are three sets of sheets / forms which can be found in the section 7 (orange) of this file. The appropriate one should be selected:

<table>
<thead>
<tr>
<th>If the patient is able to give consent, (even if only verbally or by nodding) the study should be discussed with him / her and the Research Subject Information Sheet should be given to the patient.</th>
</tr>
</thead>
<tbody>
<tr>
<td>If the patient is unable to give consent e.g. due to sedation and there is a next-of-kin. Next-of-kin should be asked if it is their opinion that the patient would not object to the study. The Next-Of-Kin Information Sheet should be given out when the study is explained.</td>
</tr>
<tr>
<td>Name of next of kin __________________________</td>
</tr>
<tr>
<td>If the patient is unable to give consent e.g. due to sedation and there is no next-of-kin, the patient must be excluded from the study.</td>
</tr>
</tbody>
</table>

Patients who have not been able to give consent themselves If at any stage, they become able to do so, the study should be explained and the Retrospective Information Sheet given out. (This should be done, even if the next-of-kin has been in agreement.) After 24 hours, retrospective consent should be obtained. If the patient is unwilling to give this, the data obtained will not be used.

Wait 24 hours then obtain consent

If the patient / next-of-kin / consultant anaesthetist is willing to proceed with the study, use the appropriate consent forms in section 8 (yellow). Three copies should be completed: one for the patient/next of kin, one for the pharmacist and one for the medical notes. A signature is required from the burns consultant (if not already taking consent) as witnessing the agreement.

If the patient is able to understand, but not able to give written consent, this must be indicated on the consent form and signed by both the consultant surgeon and a witness who understands – but is not directly involved in - the study e.g. nurse or anaesthetist looking after patient.

If consent given, enter patient Name on the patient list (Section 4 – Green) to assign study number.

Pharmacy Staff to:
Ensure patient recorded as being on study on PAS
Contact Bristol, to inform them that blood will be sent for analysis
Arrange collection with TNT
Whenever possible, prepare labels for blood tubes

Complete Patient Data Sheet (Section 6 – red)
This can be done by those approved to obtain consent. Data should relate to the day that the samples are taken. The main aim of this is to see if details such as the TBSA correlates with serum concentrations, so we may be able to advise a dose based on this in the future.

Recording dose times. It is essential that the dose times are recorded exactly. It does not matter too much if doses are not given exactly on time, but recording the exact times they are given are essential.

Both the time the drug is given and how long it was given over should be recorded for

Dose before the testing dose (i.e. night before)
Dose to be tested (i.e. 8am dose)

This should be recorded on the drug chart and patient data sheet.

Take Samples

Samples should only be taken on Mondays to Thursdays at least 24 hours after treatment has started. If samples are due to be taken when the patient is to undergo surgery where there is likely to be a significant amount of bleeding, samples should not be taken until at least the following day.

Serial blood samples will be taken by the nurse looking after the patient. For each series, six 3ml samples will be needed over one dosing interval. If a patient is on more than one antibiotic, samples should be taken over different dosing intervals.

Blood will be taken from an arterial line which has already been assigned for blood sampling using a closed, needle-free, self-sealing, access system.

Brown serum gel tubes should be used.

Samples should be clearly labelled by nursing staff with the exact time taken. Don’t worry if a sample is taken late. It is more important that we know the time.

For all antibiotics, samples should be taken:
Immediately before 8am dose
30 minutes after start of administration of dose (Therefore if a 30 minute infusion, take immediately after infusion completed)
1 hour
2 hours
4 hours

Then:
For six-hourly dose – take at 6 hours (ie immediately before next
dose)
For eight-hourly dose – take at 8 hours (i.e. immediately before next dose)
For 12 hours – take at 8 hours

In most cases, the pharmacy will have prepared pre-printed stickers for the serum tubes. Blank labels are can be found in this file if that has not been possible. After each sample has been taken, a label should be attached and the exact time blood taken to be recorded.

Ideally a member of pharmacy will take away the sample to spin straight away. If this is not possible, put the sample in the bottom of the specimen fridge in AW Theatre as soon as you can.

| Pharmacy to spin down and separate each sample |
| Check that pharmacy is aware of the time of the first dose |

| Pharmacy to package samples |

**Results**

Results will be faxed to the Pharmacy by 5pm the next day for meropenem and linezolid. The colistin assay takes 2 – 3 days. Pharmacist will advise if any dose changes are necessary.

| Dose changes |
| If a dose change is necessary, after 24 hours, a further set of samples should be taken, following the procedure as above. Please use a new checklist. |

| Adverse drug reactions |
| Although using licensed products, if the patient experiences any adverse events whilst on the antibiotic(s), this must be documented. Any SUSARs (suspected unexpected serious adverse reactions) should be reported to Sarah Dawe / Jane Allen immediately. Unexpected means that the reaction is not listed in the Summary of Product Characteristics. |
Appendix 13. Copy of Excel page for gentamicin dose calculator for pharmacists

**Aim:** to calculate the dose of gentamicin (or tobramycin) needed to achieve a peak (1 hour post dose) of 20mg/L and an aminoglycoside-free period (i.e. less than 0.5mg/L) of at least 4 hours. Round up to the nearest practical dose interval.

**Starting dose:** 7mg/kg over 30 minutes, initially once a day. Lower doses may be considered in the elderly e.g. over 70 years of age. If the actual bodyweight (ABW) of the patient is more than 20% over the ideal bodyweight (IBW), use IBW plus 40% of the excess weight.

Ideal bodyweight (IBW) in kg = 2.3 x every inch in height over 5 foot plus either 50 for a male or 45.5 for a female

Ideal bodyweight plus 40% of the excess weight = IBW plus 0.4 x (ABW - IBW)

**Sampling:** Serum samples to be taken 1 hour after the start of the infusion, then at eight hours and again at 18 hours. Ensure dose and sampling times are accurately recorded.

**Interpretation:** Medical and nursing staff are advised to contact the pharmacist for interpretation of the results. In the absence of the pharmacist (e.g. out-of-hours), they are advised to adjust serum concentrations to aim for a one-hour peak of 20mg/L (range of 16 to 25mg/L, but 20 to 25mg/L for severe infections). The dose should be proportional to the concentration e.g. If the peak serum concentration is 40mg/L, the dose should be halved. Additionally the 18-hour trough should be less than 1mg/L.

Pharmacists should use the dose calculator below to make a more accurate prediction of the required dose and frequency. The dose should be rounded off to the nearest 20mg, and the frequency usually rounded up to the nearest 12 hours.

**Example:** A 60kg patient is given a dose of 420mg. The peak concentration is 26.8mg/L (Cp1) at 1 hour (time Cp1) and at eight hours (Time Cp2) concentration is 0.4mg/L. Therefore the dose should be decreased to 320mg, and the dose interval reduced to twelve-hourly

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Weight (kg)</th>
<th>Peak Cp1 (mg/L)</th>
<th>Time Cp1 (hrs)</th>
<th>Cp2 (mg/L)</th>
<th>Time Cp2 (hrs)</th>
<th>Dose (mg) to achieve a concentration at 1 hour of 20mg/L</th>
<th>Minimum dose interval (h)</th>
<th>Vd (L)</th>
<th>Vd (l/kg)</th>
<th>k</th>
<th>Cl (l/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example</td>
<td>420.0</td>
<td>60.0</td>
<td>26.8</td>
<td>1.0</td>
<td>0.4</td>
<td>313</td>
<td>11.1</td>
<td>8.6</td>
<td>0.14</td>
<td>0.6</td>
<td>5.16</td>
</tr>
<tr>
<td>Your patient</td>
<td>360.0</td>
<td>50.0</td>
<td>20.0</td>
<td>1.0</td>
<td>5.0</td>
<td>360</td>
<td>23.6</td>
<td>14.8</td>
<td>0.30</td>
<td>0.2</td>
<td>2.92</td>
</tr>
</tbody>
</table>

Enter your patient’s details in the red font boxes in line 29 (Your patient) to determine dose and dose-interval.
NB. Pharmacists should be aware that an 8-hour concentration above 5mg/L and / or an eighteen-hour concentration above 1mg/L may indicate an increased risk of toxicity.

Remeasure peak (1 hour), eight hour and eighteen hour concentrations daily.
Monitor serum creatinine and creatinine clearance daily (ideally the creatinine clearance should be measured, not estimated by C&G equation).
Appendix 14. Survey of Drug Use in British Burns Units

Survey of Drug Use in British Burns Units

Allen J.M.,1, Melzack D.H.,2, Sanghera N.,3, Sim K.M.1
1. Queen Victoria Hospital, 2. Mount Vernon Hospital, 3. Chelsea & Westminster
e-mail jane.allen@qvh-tr.sThames.nhs.uk

Introduction
E-mail discussions between burns pharmacists have indicated that there is widely differing practice in drug therapy of burns patients. A survey of drug use was undertaken to aid the drug information role of the pharmacist and highlight areas for future research.

Method
A questionnaire was piloted, then sent to 23 burns pharmacists. Those pharmacists who had little input to burns were asked to pass on the questionnaire to a more appropriate person. The questionnaire covered the following areas of drug use: fluid resuscitation, treatment of inhalation injury, intensive care drugs, corticosteroids, antibiotics, wound care, antipruritic agents, analgesia, nutritional products and other drug use peculiar to burns management. Detailed results would be sent to all those taking part.

Results
Fifteen replies were received, a response rate of 65%. Some of the replies were incomplete. A selection of the results are presented here.

Fluid resuscitation – Adults
What fluid regimen do you use for resuscitation in major burns?

Parkland1 5
Modified Parkland (2ml/kg/BSA/ 24 hrs) 1
Muir and Barclay2 5
Other HAS based formulae 2

One unit due to change from Muir & Barclay to Parkland.
One unit uses Parkland if inhalation injury, Muir & Barclay if no inhalation injury

Inhalation injury
Please state your standard drug treatment.

Hospital Code

<table>
<thead>
<tr>
<th>Drug</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
<th>H</th>
<th>J</th>
<th>K</th>
<th>L</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylcysteine</td>
<td></td>
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<tr>
<td>Heparin</td>
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<tr>
<td>Ipratropium</td>
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<tr>
<td>Salbutamol</td>
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<tr>
<td>Normal saline</td>
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<tr>
<td>Sodium Bicarbonate</td>
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<td>Humidification</td>
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<td>Oxygen</td>
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<td>Nothing routinely</td>
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</tbody>
</table>

NB. Acetylcysteine, heparin, ipratropium, salbutamol, normal saline, sodium bicarbonate all delivered via a nebuliser.

Steroids
Do you ever use corticosteroids in sepsis?

Always / often 0
Sometimes/ Occasionally 6
Never 7

Thromboprophylaxis
Do you routinely assess patients on admission for risk of thromboembolism?

Yes 9
No 4

Vitamins, minerals and trace elements
What do you routinely give your intensive care patients?

<table>
<thead>
<tr>
<th>Vitamin/Trace Element</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
<th>H</th>
<th>J</th>
<th>K</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Nothing routinely</td>
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<td>Zinc</td>
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<td>Selenium</td>
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<td>Copper</td>
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<td>Vitamin B Co</td>
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<td>Vitamin C</td>
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<td>Multivitamins</td>
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<td>Folic Acid</td>
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</tr>
</tbody>
</table>

Antibiotics
Is your antibiotic use influenced by any of the following?

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
<th>H</th>
<th>J</th>
<th>K</th>
<th>L</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>VRE</td>
<td></td>
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<tr>
<td>MRSA</td>
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<tr>
<td>Acinetobacter</td>
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</tbody>
</table>

Discussion
This poster provides a snapshot of drug use on burns units. The full survey highlights variation in many other areas. As the information sent to those taking part includes details of all respondent hospitals, it can be used as a way to share and review practice.

References
Appendix 15. Poster Presentation. Pharmacokinetics of Meropenem in Patients with Severe Burns

Pharmacokinetics of Meropenem in Patients with Severe Burns

JM Allen¹, BS Dheansa¹, B Stewart², EL Teare³

1. Queen Victoria Hospital NHS Foundation Trust, East Grinstead, 2. Surrey and Sussex NHS Trust, 3. Chelmsford Public Health Laboratory Service
e-mail jane.allen@qvh.nhs.uk

Introduction
Previous studies have shown that standard doses of some antibiotics are sub-therapeutic in patients with major burns. This is because of altered pharmacokinetics, thought to be due to pathological changes such as major shifts of fluid and increased cardiac output in the hypermetabolic phase.

The principal aims of this study are (1) to investigate the pharmacokinetic parameters of meropenem when administered to adults patients with major burns (> 15% total burn surface area - TBSA) and (2) to produce dosing guidelines for this antibiotic. This antibiotic was selected as it is generally reserved to treat infections in seriously ill patients, and the limited data on its use in burns indicates that standard doses may result in sub-therapeutic dosing1,2. The results presented here are the first from a multi-centre study investigating the pharmacokinetics of meropenem, imipenem, colistin and linezolid.

Method
Both the decision to initiate meropenem and the dose prescribed were based on clinical need. A series of six blood samples (pre-dose, 30 minutes, 1 hour, 2 hours, 4 hours and pre-next dose) was collected after the patient had been receiving meropenem for at least 24 hours. Serum samples were then sent to Southmead Hospital, Bristol for HPLC analysis. Data were collected for future analysis. Although not directly part of the study, results were available within 24 hours. This enabled the dose to be adjusted if thought necessary, and a further set of samples could be taken.

Results
Results are presented of the first four sets of samples from two patients receiving meropenem.

Patient number 1 was a 27 year old female with 50% TBSA. She received one course of meropenem at a dose of 1g three times a day (tds) starting at day 36 post-burn (sample set 1).

Patient number 2 was 38 year old female with 70% TBSA. She received three courses: 1g tds starting 27 days post-burn (2a), 2g tds starting 55 days post-burn (2b) and 1g four times a day (qds) starting 71 days post-burn (2c). Results are shown in the table below.

<table>
<thead>
<tr>
<th>Sample set number</th>
<th>Peak Serum Concentration (mg/L)</th>
<th>Trough Serum Concentration (mg/L)</th>
<th>Half-life (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14</td>
<td>0.8</td>
<td>1.8</td>
</tr>
<tr>
<td>2a</td>
<td>21</td>
<td>0.3</td>
<td>1.2</td>
</tr>
<tr>
<td>2b</td>
<td>79</td>
<td>3.3</td>
<td>1.7</td>
</tr>
<tr>
<td>2c</td>
<td>27</td>
<td>1.1</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Discussion
In this study, all meropenem peak serum concentrations were below published data where bolus doses of 1g resulted in peaks of between 94 and 112mg/L3. Trough levels were similar to those expected4.

In all cases, the half-life was longer than the average of 0.66 hours measured for 14 subjects following a 1g infusion of meropenem over 30 minutes 4.

Serum concentrations of meropenem in study patients compared with data for healthy volunteers

Animal studies have shown that for meropenem to be effective, the serum concentration must be above the minimum inhibitory concentration (MIC) for 33 - 40% of the dosing interval4. Other studies of beta-lactam antibiotics have found that the time above the MIC for efficacy is 40 to 50%. Taking the MIC as the breakpoint (4mg/L)5, when meropenem was given in the standard dose of 1g three times a day the time above the MIC was approximately 31% and 33%, so may have been subtherapeutic. When the higher doses were given, time above the breakpoint was greater than 50% of the dosing interval.

Conclusion
Initial results indicate that standard doses of meropenem may result in subtherapeutic serum concentrations in patients with severe burns.

Other burns centres are invited to participate in this study. Please contact Jane Allen by email.

References
3. Astra-Zeneca – Summary of Product Characteristics

Pharmacokinetics of Meropenem in Adults with Major Burns

Allen JM¹, Dheansa BS¹, James SE², Hanlon GW², Davies JG³, Stewart BA⁴ 1. Queen Victoria Hospital NHS Foundation Trust, East Grinstead, 2 University of Brighton, 3. Kings College, London 4. Surrey & Sussex NHS Trust

Introduction
Physiological changes that occur with a major burn injury result in altered pharmacokinetics of some drugs. Previous studies have suggested the need for increased doses of some antibiotics to be efficacious. The aim of this study was to determine whether the standard dose of meropenem was sufficient to treat likely pathogens in adult patients with severe burns. An objective of the study was to calculate pharmacokinetic parameters and compare them with those published for healthy volunteers, on whom dose recommendations are made.

Methods
Adults with burns >15% total burn surface area (TBSA) who were receiving meropenem to treat infection were included in the study. For each patient a series of blood samples were taken over one dosing interval and the results analysed. The marker of efficacy selected was for the serum concentrations to be above the breakpoint of 4mg/L for at least 40% of the dosing interval. Pharmacokinetic parameters were calculated using WinNonlin®.

Results
Seven patients were recruited to the study. The table below shows patient demographics plus estimated percentage of dose interval where serum concentrations were above breakpoint and calculated pharmacokinetic parameters for the starting dose of 1g eight-hourly. Pharmacokinetic parameters were significantly different from those published for healthy volunteers.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age</th>
<th>TBSA (%)</th>
<th>&gt; 40% of dose interval above 4mg/L?</th>
<th>Elimination rate constant</th>
<th>Half-life (h)</th>
<th>Volume of Distribution (L)</th>
<th>Clearance (L/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>27</td>
<td>50</td>
<td>N (33%)</td>
<td>0.31</td>
<td>2.2</td>
<td>81</td>
<td>25</td>
</tr>
<tr>
<td>F</td>
<td>38</td>
<td>70</td>
<td>N (35%)</td>
<td>0.56</td>
<td>1.2</td>
<td>40</td>
<td>22</td>
</tr>
<tr>
<td>M</td>
<td>62</td>
<td>32</td>
<td>Y (81%)</td>
<td>0.25</td>
<td>2.8</td>
<td>47</td>
<td>12</td>
</tr>
<tr>
<td>M</td>
<td>73</td>
<td>34</td>
<td>Y (100%)</td>
<td>0.17</td>
<td>4.0</td>
<td>43</td>
<td>7</td>
</tr>
<tr>
<td>M</td>
<td>45</td>
<td>20</td>
<td>N (28%)</td>
<td>0.34</td>
<td>2.1</td>
<td>92</td>
<td>31</td>
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<tr>
<td>M</td>
<td>35</td>
<td>80</td>
<td>N (23%)</td>
<td>0.49</td>
<td>1.4</td>
<td>85</td>
<td>42</td>
</tr>
<tr>
<td>M</td>
<td>37</td>
<td>35</td>
<td>N (30%)</td>
<td>0.94</td>
<td>0.7</td>
<td>14</td>
<td>13</td>
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</tbody>
</table>

Discussion and Conclusions
This study shows that meropenem has altered pharmacokinetics in patients with major burns, when compared with data published for healthy volunteers. Some patients may require an increased dose to treat likely burns pathogens. Further work is required to develop dosage guidelines for this group of patients.
Appendix 17. Potential Sub-therapeutic Linezolid and Meropenem Antibiotic Concentrations in a Patient With Severe Burns and Sepsis


Hallam MJ, Allen JM, Dheansa BS, James EJ, Hanlon GW, Davies JG, Donaldson PMW

Altered pharmacokinetics in patients with major burns may result in serum antibiotic concentrations below those required to be effective against the common pathogens encountered in burns patients. The major changes in the fluid volumes of key body compartments, which occur with a large burn, may increase the apparent volume of distribution of a drug, thereby lowering its concentration when a standard dose is given. In addition, the observed increase in renal blood flow reported in burns patients, because of the change in cardiac output, may result in a higher drug clearance and a shorter elimination half-life. As a consequence, studies have recommended higher doses or more frequent dosing or both for some antibiotics in patients with major burns, but data are lacking for many of the antibiotics reserved for treatment of life-threatening infections. The authors measured serum concentrations of two antibiotics, linezolid and meropenem, in an immunosuppressed patient who presented with a severe burn to determine whether therapeutic concentrations were achieved, thereby improving the likelihood of infection control.

Introduction

Altered pharmacokinetics in patients with major burns may result in serum antibiotic concentrations below those required to be effective against the common pathogens encountered in burns patients\(^1\). The major changes in the fluid volumes of key body compartments which occur with a large burn may increase the apparent volume of distribution of a drug, thereby lowering its concentration when a standard dose is given. Additionally the observed increase in renal blood flow reported in burns patients, due to
the change in cardiac output, may result in a higher drug clearance, and a shorter elimination half-life. As a consequence studies have recommended higher doses and/or more frequent dosing for some antibiotics in patients with major burns\textsuperscript{2-4} but data are lacking for many of the antibiotics reserved for treatment of life-threatening infections. We measured serum concentrations of two antibiotics, linezolid and meropenem, in an immunosuppressed patient who presented with a severe burn to determine whether therapeutic concentrations were achieved, thereby improving the likelihood of infection control.

**Case report**

A 27-year-old man, injured in a caravan fire following the explosion of a gas cooker sustained burns to his face, neck, trunk, legs, and arms totalling 52% total body surface area. The patient was taken to a local university hospital for assessment where his injuries necessitated intubation, ventilation, and subsequent transfer to the Queen Victoria Hospital Burn Centre.

The burns were of mixed depth and the patient was taken immediately to the operating theatre for debridement and application of Biobrane\textsuperscript{™} to his limbs and Aquacel\textsuperscript{®} Ag to the neck. Post-operatively he was managed in the burns intensive care unit.

Forty-eight hours post-injury the patient began to show signs of sepsis with pyrexia, deteriorating respiratory function, and increasing cardiovascular instability which required fluid replacement and the commencement of inotropic support. A provisional diagnosis of lobar pneumonia was confirmed by subsequent chest x-ray indicating a right lower lobe consolidation. He was commenced on 4.5g of piperacillin and tazobactam (Tazocin\textsuperscript{®}) four times a day following advice from our resident consultant microbiologist (Table 1).

Following a seven-day course of piperacillin and tazobactam, the patient continued to experience persistent respiratory difficulties associated with a pyrexia of 40 degrees and on-going elevation of his C-reactive protein (CRP) and white blood cell (WBC) counts (18.33 x10\textsuperscript{9}/L and 308mg/L respectively). Repeat chest x-ray showed bilateral consolidation and the patient’s left foot burns had also become infected. A full range of
Swabs were sent for cultures and sensitivities, the results revealing an array of microorganisms (see Table 1).

<table>
<thead>
<tr>
<th>Culture site</th>
<th>Organism isolated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sputum</td>
<td><em>Candida albicans</em></td>
</tr>
<tr>
<td>Peripheral swabs</td>
<td><em>Candida albicans</em></td>
</tr>
<tr>
<td></td>
<td><em>Corynebacterum spp</em></td>
</tr>
<tr>
<td></td>
<td><em>Bacillus cereus</em></td>
</tr>
<tr>
<td></td>
<td><em>Enterococcus spp</em></td>
</tr>
<tr>
<td></td>
<td><em>Klebsiella oxytoca</em></td>
</tr>
<tr>
<td></td>
<td><em>Enterobacter cloacae</em></td>
</tr>
<tr>
<td></td>
<td><em>Stenotrophomonas maltophilia</em></td>
</tr>
<tr>
<td>Tracheostomy site</td>
<td><em>Coagulase negative Staphylococcus</em></td>
</tr>
<tr>
<td></td>
<td><em>Candida albicans</em></td>
</tr>
<tr>
<td>Blood cultures</td>
<td>Negative for organisms</td>
</tr>
<tr>
<td>Central line catheter tip</td>
<td><em>Candida albicans</em></td>
</tr>
</tbody>
</table>

Table 1: Summary of microbiological results for the patient showing all cultured organisms.
Following further microbiological consultation piperacillin and tazobactam was stopped on day 8 and a course of meropenem commenced at the standard eight-hourly dosage regimen. There was minimal response to this antibiotic after four days with little improvement in the patient's physiological and biochemical profiles, so that, on day 12 linezolid and metronidazole were added. Serum concentrations of both meropenem and linezolid were then measured. The samples were taken pre-dose, then at 30 mins, 1 hour, 2 hours, and 4 hours post dose. The final sample was taken pre-the next dose for meropenem and at 8 hours for the linezolid. Serum assays were analysed by the use of high performance liquid chromatography (HPLC). The marker for efficacy selected for both antibiotics was for serum concentrations to be above the breakpoint of 4mg/L for a minimum of 40% of the dosing interval\textsuperscript{5, 6}.

Antibiotic concentrations were measured on day 13 for meropenem and day 14 for linezolid. Both were found to be low and dose frequencies were increased as shown in Figure 1.

<table>
<thead>
<tr>
<th>Day</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
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<th>14</th>
<th>15</th>
<th>16</th>
<th>17</th>
<th>18</th>
<th>19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piperacillin / Tazobactam</td>
<td>4.5g</td>
<td>6-hourly</td>
<td>1g</td>
<td>8-hourly*</td>
<td>1g</td>
<td>4-hourly**</td>
<td>1g</td>
<td>4-hourly**</td>
<td>1g</td>
<td>4-hourly**</td>
<td>1g</td>
<td>4-hourly**</td>
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<td>4-hourly**</td>
<td>1g</td>
<td>4-hourly**</td>
<td>1g</td>
</tr>
<tr>
<td>Meropenem</td>
<td>1g</td>
<td>8-hourly*</td>
<td>1g</td>
<td>4-hourly**</td>
<td>1g</td>
<td>4-hourly**</td>
<td>1g</td>
<td>4-hourly**</td>
<td>1g</td>
<td>4-hourly**</td>
<td>1g</td>
<td>4-hourly**</td>
<td>1g</td>
<td>4-hourly**</td>
<td>1g</td>
<td>4-hourly**</td>
<td>1g</td>
<td>4-hourly**</td>
<td></td>
</tr>
<tr>
<td>Linezolid</td>
<td>600mg</td>
<td>12-hrly</td>
<td>600mg</td>
<td>12-hrly</td>
<td>600mg</td>
<td>12-hrly</td>
<td>600mg</td>
<td>12-hrly</td>
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<td>Metronidazole</td>
<td>500mg</td>
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<td>8-hourly</td>
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<td>8-hourly</td>
<td>500mg</td>
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<td>500mg</td>
<td>8-hourly</td>
<td>500mg</td>
<td>8-hourly</td>
<td></td>
</tr>
</tbody>
</table>

* Meropenem was commenced at a dose of 500mg 8-hourly but increased to 1g 8-hourly after 2 doses, as the infection was considered to be severe.
** Meropenem dose frequency was increased to 6-hourly on day 14, but on further consideration to 4-hourly on day 15.

Serum concentrations were measured again once sufficient time had passed for steady-state conditions to be achieved. The percentage of the dose interval above 4mg/L at the different dosing regimens is shown in table 2.

On day 15 of antibiotic therapy the patient had not improved clinically, still requiring a high level of ventilatory support, remaining persistently pyrexial, and suffering rigors. Additionally, his inflammatory markers and white blood cell counts remained elevated.
Following the increased frequency of dosing of both meropenem and linezolid on day 15 there was a steady improvement in the patient’s condition, with a reduction in his pyrexia and improved respiratory function. By day 16 of therapy the patient was apyrexial, cardiovascularly stable, his CRP and white counts had reduced significantly (36mg/L and 13.55 x10⁹/L respectively), and was only requiring minimal ventilatory support with spontaneous respiration. The continued improvement in the patient’s general condition and mobility resulted in a successful tracheostomy tube decannulation later that day and the cessation of antibiotic therapy on day 19. The patient remained well and was discharged following a 28 day admission.

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dose</th>
<th>% of dose interval above 4mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meropenem</td>
<td>1g 8-hourly</td>
<td>30%</td>
</tr>
<tr>
<td>Meropenem</td>
<td>1g 4-hourly</td>
<td>75%</td>
</tr>
<tr>
<td>Linezolid</td>
<td>600mg 12-hourly</td>
<td>20%</td>
</tr>
<tr>
<td>Linezolid</td>
<td>600mg 8-hourly</td>
<td>75%</td>
</tr>
</tbody>
</table>

Table 2: Results showing percentage time above the breakpoint

Discussion

Pharmacodynamics (PD) is the relationship between serum concentration of and the pharmacological and toxicological effects of drugs. Pharmacokinetics (PK) describes the processes involved in the absorption, distribution, metabolism and elimination of drugs. Thus the efficacy of antibiotics are related to both PK and PD, but the actual measure used varies according to the class of antibiotic.

The three most common measures of antibiotic efficacy are the length of time it remains above the minimum inhibitory concentration (T>MIC), the ratio of the peak drug concentration to the MIC (Cmax/MIC), and the ratio of the area under the concentration-time curve at 24 hours to MIC (AUC0-24: MIC). In addition to the PK-PD measure, bactericidal activity of an antibiotic is also related to its post-antibiotic effect (PAE), the persistent suppression of bacterial growth following exposure to an antimicrobial.
The efficacy of meropenem is dependent on T>MIC\textsuperscript{9, 10}. The percentage of time is lower for meropenem that other beta-lactams, which is thought to be due to a more prolonged PAE. For bacteriostasis, the concentration should exceed 20% of the dosing interval, but for near-maximal bactericidal effects, this figure is 40%\textsuperscript{11}. As MICs of pathogens are not measured as part of routine clinical practice, the breakpoint of 4mg/L was selected, as all bacteria testing as sensitive have an MIC of 4mg/L or less\textsuperscript{12}.

Linezolid is also a time-dependent antibiotic with a persistent PAE. The PK-PD indices of T>MIC and AUC\textsubscript{0-24}: MIC have both been identified as a measure of its efficacy\textsuperscript{11}. A percentage of time of 40% above the MIC achieved significantly enhanced bacterial killing \textit{in vitro} and was predictive of outcome \textit{in vivo}\textsuperscript{13, 14}. Whilst current thinking may be that AUC\textsubscript{0-24}: MIC is a better indicator of outcome, for ease of clinical interpretation we used the T>MIC of more than 40% as our measure, again using the breakpoint of 4mg/L in the absence of knowing the MICs\textsuperscript{15}.

This case suggests that burn patients receiving meropenem and linezolid at standard doses may not be achieving adequate antibiotic serum concentrations. Further work is required to develop dosing guidelines in this patient population.

\textbf{References}