Pharmacokinetics of antibiotics in burn patients

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Drug pharmacokinetics are significantly altered in the burned patient but the interplay of a large number of variables is involved in deciding how an individual will deal with a drug. Consequently the burn patient population shows significant inter- and intrapatient variation. In 1976 altered aminoglycoside pharmacokinetics and the need for increased dosage in burn patients was reported but, despite this early study, a review of the currently available literature shows that for many drugs there is a paucity of information to support current dosage recommendations. In addition, many reports are based upon small numbers of patients, and even in larger studies there is no standardization of the study population with regard to the important variables known to affect drug handling. For the sub-population of burn patients who eliminate drugs extremely rapidly, a concern exists over the adequacy of antibiotic dosing. It is suggested that antibiotic serum concentrations be measured for all drugs in every patient to ascertain whether there is a significant problem with dosing. Additionally, future pharmacokinetic studies need to be standardized in burn patients.

Introduction

The pharmacokinetics of drugs may be significantly altered in burn patients, as is readily observed, for instance, in the much shorter duration of action of anaesthetic agents. The effect of the thermal insult upon drug pharmacokinetics is complex and for some drugs not completely understood. In pharmacokinetic terms, however, the pathological changes that occur in burns patients may be broadly divided into two phases. In the acute phase of the injury, lasting for approximately 48 h, protein-rich fluid is lost from the vascular system as a result of altered capillary permeability. In large burns, the release of blood-borne vasoactive substances means that such capillary changes occur diffusely throughout the body. The resultant hypovolaemia leads to a drop in cardiac output and tissue hypoperfusion including reduced renal blood flow and a fall in glomerular filtration rate (GFR).

During the second hypermetabolic phase (beyond 48 h after the thermal injury) the characteristic change, provided that adequate fluid replacement has occurred, is an increased cardiac output, with concomitant increased blood flow to the kidneys and liver. Thus, there is an increase in the GFR, as assessed by creatinine clearance. Creatinine clearance may indeed not only return to normal but may become significantly elevated compared with healthy controls. Tubular function can be depressed in the hypermetabolic phase despite the increased renal perfusion. Liver blood flow is also significantly increased during this phase. The effect on drug metabolism is diverse: there is an acute depression in microsomal activity, but conjugative metabolic activity is unaffected or increased. The changes associated with the hypermetabolic phase evolve over several days, and their intensity will vary with time. Hence the physiological changes in a burned patient on day 3 or 4, for example, may be quite different from those on day 8. A multitude of other factors can influence the final outcome on renal clearance of drugs after a burn, for example. They include pre-existing cardiovascular or renal disease (from, for example diabetes), inadequate renal perfusion during resuscitation, sepsis and administration of potentially nephrotoxic agents. The end result is a high degree of interpatient variability in renal function, and hence a high degree of interpatient variability might be expected with antibiotic handling.

Burn injury also causes considerable changes in plasma protein levels. In general, patients exhibit decreased albumin and increased α1-acid glycoprotein levels. These changes can influence the need for loading doses of highly-bound drugs, but are generally of relatively minor importance in the design of maintenance dosing regimens for most antimicrobial agents.

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Design of pharmacokinetic studies in burn patients

There appears to be little in the way of standardization of the burn patient population when pharmacokinetic studies of antibiotics are undertaken. For example, some studies on antibiotics have predominantly included patients in the acute phase of injury (when sepsis is rare). The drug pharmacokinetics are significantly different to those in the hypermetabolic phase (when sepsis predominantly occurs). Furthermore, antibiotic pharmacokinetics in paediatric patients may be significantly different from adults, yet the results of both groups are often combined. Finally, studies undertaken during the prophylactic use of antibiotics may yield different results from those performed when antibiotics are used to treat infection, as sepsis is known to alter drug pharmacokinetics.

Whilst these three points should easily be overcome, it is important to recognize that burns patients are an extremely heterogeneous group with significant inter- and intra-patient variation with regards to drug handling. The danger with any study lies with the possibility that it will not be truly representative of the whole population. This is particularly so with small studies.

A large number of factors affect drug handling in burn patients (Table) and it is not possible to standardize for each of these variables, but studies should be of sufficient size to be representative. Efforts should concentrate on those factors likely to have a major effect on drug handling, e.g. ensuring patients with widely differing GFRs (including those with greatly elevated values) are part of any study. The analysis of antibiotic efficacy must also ensure that, in every patient, the antibiotic achieves therapeutic concentrations.

Studies in burns patients should be scrutinized against the variables outlined above.

Indications for antibiotic therapy

The thermal injury that destroys the skin will also render the wound devoid of the cutaneous bacterial flora. Within a short period of time, however, unless this burn wound can be excised and closed by early tangential excision, colonization is inevitable. Topical antiseptics are usually applied to the raw areas in an attempt to reduce the number of re-colonizing flora to a level below which invasive infection takes place. Routine prophylactic systemic antibiotics are not indicated immediately.

Antibiotic therapy is reserved for when there is clinical evidence of infection, which is usually lower respiratory tract infections (especially following inhalational burns), infections of intravascular cannulae or wound infections. For the large burn, when sepsis is clinically diagnosed, broad-spectrum antibiotic therapy is initiated, the specific choice based on the results of surveillance cultures and knowledge of antibiotic resistance in the unit. The antibiotic spectrum should be sufficient to cover staphylococci, streptococci and Gram-negative facultative anaerobes as well as Pseudomonas aeruginosa and Acinetobacter spp. Initial empirical antibiotic therapy may be modified later according to culture results. The isolation of Streptococcus pyogenes from burned skin should always be an indication for treatment, irrespective of the patient’s condition.

Prophylactic antibiotics are often given when debridement of large contaminated burns is required, although there is little evidence to support this practice.\(^3\) Prophylactic antibiotics may, however, be justified during an outbreak of S. pyogenes infection.

Aminoglycosides

Aminoglycosides are indicated for the treatment of burn patients either as part of empirical therapy or for established Gram-negative sepsis. For difficult to treat organisms, such as P. aeruginosa, they should be used in combination with another agent. As discussed below, the failure of conventional dosing regimens to achieve therapeutic levels is well recognized, such that some centres avoid their use; however, this need not be the case.

Pharmacokinetic studies

In 1976, Zaske et al.\(^5\) first described altered antibiotic pharmacokinetics in burn patients, demonstrating the need for a much increased gentamicin dosage. In comparison with non-burn patients, who require a dosage of 3–5 mg/kg/day, in their study\(^6\) and one later one,\(^6\) the mean daily dose required to keep concentrations in the therapeutic range in burn patients was 7.4 mg/kg/day and 11.2 mg/kg/day, respectively. However, the variation in individual dosage requirements was immense, ranging from 2.1 to 16.8 mg/kg/day and 3.9 to 17.8 mg/kg/day in the respective studies. There was no single factor of a large number of variables, e.g. age, burn size and renal function, that correlated with the altered aminoglycoside requirement, and that could be used to predict the changes in dosage required to attain therapeutic concentrations.

Gram-negative septicaemia in burn patients is associated with a high mortality, and rapid attainment of therapeutic peak levels is associated with improved outcome.\(^7,8\)

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Table. Variable factors that affect drug pharmacokinetics in burned patients

<table>
<thead>
<tr>
<th>Size of burn</th>
<th>Depth of burn</th>
<th>Age</th>
<th>Time since burn injury</th>
<th>Creatinine clearance</th>
<th>Serum protein levels</th>
<th>State of hydration</th>
<th>Presence of sepsis</th>
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Pharmacokinetics of antibodies in burn patients

Therein lay a problem in burn patients as conventional aminoglycoside dosing, by trial and error, resulted in an unacceptable delay in achieving adequate levels. An alternative way of dosing burn patients was required.

If there was no certain way to predict how an individual would handle an aminoglycoside, the alternative was to measure the pharmacokinetics in each patient. In 1978, Zaske et al. described the rapid individualization of the gentamicin dosage regimen in 66 burns patients by means of first dose pharmacokinetics. Each patient received an initial gentamicin dose of 1.0–1.7 mg/kg. Serum samples were collected at 15 min, and 1 and 3 h post-infusion. Results were plotted to provide estimates of gentamicin half-life and distribution volume in each patient, and a new gentamicin dosage, individualized to that patient, was calculated. Thirty-six to 48 h later, peak and trough concentrations were measured in 47 of the 66 patients. The mean (± s.d.) peak concentration was 7.6 (± 0.9) mg/L and the mean trough concentration was 1.4 ± 0.8 mg/L. In this way the regimens could be individualized within the initial 12–18 h of treatment.

Hollingsed et al. also used first dose (FD) pharmacokinetics in a study published in 1993. They compared retrospectively the results in 12 patients treated using FD pharmacokinetics with 14 patients in whom conventional dosing methods had been used. Plasma concentrations were measured before and after the third dose, and satisfactory concentrations were defined as follows: for gentamicin a peak of 5–10 mg/L and a trough of 0.5–2 mg/L, and for amikacin a peak of 20–30 mg/L and a trough of 4–8 mg/L. Of the five treatment failures that occurred in the FD group, one had, by their criteria, a sub-therapeutic peak concentration: the remaining four had sub-therapeutic trough concentrations. In the conventionally-adjusted group, 13 of 15 had sub-therapeutic peak concentrations, with some patients never achieving a satisfactory peak concentration during a 7–10 day course of therapy. These authors chose an unusual definition of therapeutic concentrations: aminoglycosides exhibit concentration-dependent killing, making peak concentrations the best guide to therapeutic efficacy. Trough concentrations are a better guide to drug toxicity and do not relate to therapeutic efficacy.

In 1991, Zaske et al. proposed a simplified dosing regimen to assist clinicians in obtaining therapeutic concentrations, after initial doses of gentamicin in patients with normal renal function. The dosage and dosing intervals were adjusted according to four age groups—0–10 years, 11–30 years, 31–60 years and >60 years. The results obtained with this method were not as accurate as those achieved by FD pharmacokinetics but it was meant to provide a more pragmatic approach.

In non-burned patients there has been a move to od aminoglycoside dosing. This is possible because aminoglycosides exhibit concentration-dependent killing and a post-antibiotic effect. The od regimen also has the potential for less renal toxicity, as this is not concentration dependent. Hoey et al., using pharmacokinetic data obtained from 52 burn patients previously treated with an aminoglycoside, estimated the peak concentration and aminoglycoside-free interval for simulated od dosage regimens of 5 and 7 mg/kg/day. As would be expected from fixed dosing, there was a wide spread of results—some patients having trough concentrations <0.1 mg/L as early as 7.5 h after the dose, giving a drug free period of >12 h. At the other extreme in some patients, the drug concentration never fell below 0.1 mg/L during the 24-h period. In conclusion, these authors suggested that it might be necessary to individualize even od aminoglycoside therapy in burn patients.

In summary, rapid attainment of therapeutic aminoglycoside concentrations can be achieved in burn patients using FD pharmacokinetics. Judicious use of larger initial doses of aminoglycoside (1.0–1.7 mg/kg and 3 mg/kg of gentamicin were cited in the two papers) might attain therapeutic concentrations even more rapidly. My own practice, in a limited number of patients with normal renal function, is to give an initial dose of gentamicin 5 mg/kg and to measure a peak plasma concentration 1 h later, to ensure a therapeutic concentration is reached. The plasma concentration is then measured approximately 7 h post-dose and if this is <1 mg/L a further 5 mg/kg of gentamicin is administered. Seven hours later still the concentration is checked and 5 mg/kg administered if this is <1.0 mg/L. Where the plasma concentration is >1.0 mg/L at 7 h, a further dose is withheld until the trough concentration has fallen below 1 mg/L. The exact time the concentration is repeated in these instances will depend on how much greater than 1 mg/L the result is. With this method, one can rapidly arrive at daily dosage of between 5 and 15 mg/kg of gentamicin (most patient dosages will fall within these values).

Do aminoglycosides need to be used to treat burns? My own experience is that there is often no choice, because of resistance to other agents. Secondly, there is evidence from the treatment of other immunocompromized patients that the combination of an aminoglycoside with a β-lactam antibiotic is beneficial.

Glycopeptides
Methicillin-resistant Staphylococcus aureus (MRSA) is endemic in most burn units, and when invasive infection occurs glycopeptides are usually the drugs of choice. They are also indicated in the treatment of other severe Gram-positive infections (e.g. S. pyogenes and methicillin-sensitive S. aureus) if β-lactams are contraindicated owing to allergy.

Vancomycin
Rybak et al. evaluated the pharmacokinetics of vancomycin in 10 burn patients, 14 iv drug abusers and 10
controls. The size of the burns was >10% total body surface area, the time post-burn that antibiotic therapy was initiated ranged from 7 to 15 days, and the mean creatinine clearance was 111.0 ± 28.3 mL/min. Creatinine clearance and vancomycin clearance were significantly elevated in burns patients compared with the other two groups. The increased clearance appeared to be due to both raised glomerular filtration and increased tubular secretion. There was a reasonable correlation (r² = 0.77) between creatinine clearance and vancomycin clearance. The total daily vancomycin dosage in the three groups ranged from 2 to 6 g/day (28.9–42.7 mg/kg bodyweight), 30 mg/kg being the standard recommended dose for non-burn patients. That burns patients require higher and more frequent dosing has been confirmed in other studies.13,14

The traditional method of vancomycin administration has been challenged in both non-burn and burn patients. Conventional practice is to give vancomycin by short infusion, two to four times per day, and to measure peak and trough levels. This is similar to aminoglycoside dosing and the characteristics of aminoglycosides, namely concentration-dependent killing with toxicity related to high trough levels, favour this method of administration. Vancomycin, on the other hand, does not share these characteristics. Bacterial killing is not concentration dependent, but is a function of time and the maintenance of antibiotic concentration at or above approximately four times the MIC. In terms of toxicity there is no conclusive evidence that this is related to serum levels.15

In theory, administration of vancomycin by continuous infusion (CI) might better match the drug’s characteristics, resulting in cidal activity being maintained throughout the dosing interval. With conventional dosing (CD), the high peaks confer no extra bactericidal activity, but when the serum concentrations fall below c. 4 × MIC, cidal activity is lost.

James et al.16 compared CD and CI vancomycin therapy in 10 non-burn patients with suspected or documented Gram-positive infections. Patients were randomized to receive either CD or CI therapy for 2 consecutive days and then the opposite regimen for a further 2 days. Serum samples for analysis were obtained on the second day of each therapy. Part of the analysis included measurement of serum bactericidal titres (SBT) against a methicillin-sensitive S. aureus and a methicillin-resistant S. aureus (MRSA). Overall, both regimens resulted in the MIC being exceeded 100% of the time. Although statistically there was no difference in any measured parameter between the two treatments, trough SBTs remained >1:8 for 100% of the time after CI therapy versus 60% of the time for CD therapy. The clinical impact of this result is unknown. The authors concluded that CI therapy should be further examined to determine the clinical efficacy of this method of administration of vancomycin.

Concil et al.17 looked at CI of vancomycin in 18 burn patients with a mean burn surface area of 40%. Their average age and weight were 44 years and 63.4 kg, respectively. Details of creatinine clearance were not given. Patients with hepatic or renal impairment and those without a central line were excluded. Vancomycin was administered at an initial dose of 35 mg/kg for the treatment of either documented or suspected wound infection or septicemia. Therapy was combined with another anti-staphylococcal agent in every case. The target vancomycin concentration was ≥15 mg/L, but measurement of vancomycin concentrations on day 3 showed 80% of cases to be below this value. The only patients with adequate levels were those >58 years of age. Eleven patients required an increase in dose to at least 40 mg/kg/day to achieve the target value. In only two cases was the vancomycin dose reduced. Continuous infusion of vancomycin was tolerated well and there was no evidence of an adverse effect on renal function. In four patients, there was a transient rise in serum alanine aminotransferase concentrations. The authors’ rationale for a target value of ≥15 mg/L was based on several factors. First, rifampicin resistant isolates have emerged previously when this drug was administered in conjunction with vancomycin, and the trough vancomycin level fell below 15 mg/L.18 Secondly, a serum concentration of vancomycin of at least four times the MIC should be maintained. If the MIC for a sensitive strain is ≤4 mg/L, this would equate to a serum concentration of 16 mg/L. Finally, even if the MIC for most staphylococci lies between 1 and 2 mg/L, other authors have recommended plasma concentrations of ≥15 mg/L since they believe that in order to achieve adequate tissue levels, values of 6–10 times the MIC are required,29,20 and that the upper limit for vancomycin serum concentrations should be approximately 23 mg/L. This is based upon a study by Wysocki et al.21 who found that seven out of 29 patients developed a reduced creatinine clearance and a rise in serum creatinine levels. These patients were those who not only had a long duration of treatment (>20 days) but also had serum vancomycin concentrations of 46 ± 24 mg/L. In the other patients, who had serum concentrations of 23.4 ± 3.8 mg/L, no diminution of renal function was observed.

As vancomycin levels are routinely measured, the necessity for administering larger doses to burns patients should be apparent. The outstanding questions are whether CI is the preferred method of administration and, if so, what is the target serum concentration.

**Teicoplanin**

Steer et al.22 studied the pharmacokinetics of a single dose of teicoplanin (12 mg/kg/day) in 15 adults and five children. Teicoplanin was administered within 48 h of admission in 12 adults and two children. The average burn size in adults was 30% (range, 15–60%) and in children 15% (range, 10–30%). Measurements of creatinine clearance were not given but the clearance of teicoplanin was significantly greater (per kg bodyweight) in children than in adults. A
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The serum concentration of teicoplanin of >4 mg/L was maintained for 24 h after a single iv dose. Considerable variation between individuals was noted. No significant correlation between age, percentage area of burn, serum creatine concentration or teicoplanin concentration was noted in adults. The authors concluded that a single dose of 12 mg/kg was sufficient to produce adequate serum concentrations for 24 h in the patients studied. Serum monitoring was advised in children (as excretion was more rapid) and others with ‘high total clearance’ (although no recommendation was made as to how patients with a ‘high total clearance’ could be identified).

Potel et al. studied 21 adult burns patients alongside five healthy controls. The burns patients were divided into two groups; group I comprising 10 patients with a burned surface area of 25–30% and group II, 11 patients with a burned surface area of >40%. Both groups of patients were given a single dose of teicoplanin, 10 mg/kg body-weight at the following times post-burn: 2–3 days, 8–10 days and 15–18 days. Creatinine clearance ranged from 20 mL/min to 160 mL/min. Trough serum concentrations of teicoplanin at 12 h were consistently less than 8 mg/L in all groups. The authors concluded that burned surface area and time post-burn could not be used to predict the most appropriate dose. Serum concentrations after 12 h showed that a second daily dose was required in all groups. In burn patients with a high creatinine clearance (>140 mL/min), careful monitoring was recommended to avoid low trough levels.

Lesne-Hulin et al. reported a single case of a 19-year-old man, weighing 60 kg, who was admitted to an intensive care unit with 60% burns, half of which were full thickness. Ten days after admission, the isolation of MRSA from both a skin biopsy and central venous catheter culture prompted antibiotic therapy with teicoplanin and sodium fusidate. Teicoplanin was initially administered at 12 mg/kg every 12 h for the first 24 h and then changed to 12 mg/kg/day. A trough level measured at day 5 of therapy was 8 mg/L. Their target trough level was between 12 and 15 mg/L. Teicoplanin dosage was therefore increased to 15 mg/kg and then to 20 mg/kg giving trough levels on day 8 of 9.6 mg/L and on day 15 of 8.9 mg/L. The patient’s creatinine clearance at day 16 was elevated, at 240 mL/min. Pharmacokinetic studies were performed on day 16. In comparison with data from five healthy subjects, the burn patient showed a significant (>5 times) increase in total clearance. This was due to enhanced renal clearance and some loss through the burn wound.

Although the patient clinically improved after 5 days of therapy, because he was on combination therapy it is not possible to comment on the adequacy of teicoplanin dosage from a clinical standpoint. It is also not clear how long after the change in dosage to 20 mg/kg/day teicoplanin concentrations were measured: levels may take some time to equilibrate.

The consensus from the first two studies is that there is a wide interpatient variation in burns patients and a need to monitor levels. Potel et al. suggesting this in patients with a creatinine clearance of >140 mL/min, and Steer et al. recommending it in children and others with ‘high total clearance’. Even then, some patients with a low creatinine clearance might be at risk of subtherapeutic concentrations of teicoplanin as the correlation between excretion and creatinine clearance was not absolute. However, there is disagreement over dosage: Steer et al. found 12 mg/kg to be adequate, but they almost exclusively studied patients in the acute phase when renal function is known to be impaired (no data on creatinine clearance were supplied). Potel et al. did study patients in both the acute and hypermetabolic phases and found 10 mg/kg to be inadequate, but this dosage was also found to be insufficient in a control group of normal individuals. The discrepancy over dosage recommendations predominantly depends upon which trough concentration is targeted. Steer et al. selected a 24-h trough value of 4 mg/L, arguing that 90% of strains of S. aureus are inhibited at teicoplanin concentrations of 0.2–3.1 mg/L. Potel and coworkers’ target 24-h trough value was 8 mg/L although a value of 10 mg/L (similar to vancomycin) was also suggested. In the case report by Lesne-Hulin et al. the target value was 12–15 mg/L. Wilson & Grunenberg recommend a trough value of 15 mg/L teicoplanin for staphylococcal infection, except endocarditis where 20 mg/L is suggested. As already stated, the patient with a large burn is immunocompromised and a target minimum trough level of 15 mg/L in moderate or severe staphylococcal infection (excluding endocarditis) would seem reasonable. The studies of Steer et al. and Potel et al. are both atypical, in that by administering a single dose of teicoplanin they do not reflect the recommended practice of giving a loading dose. It is usual for three doses to be given in the initial 48 h period of treatment and adherence to this dosing regimen would be expected to produce higher trough levels.

In summary, it would seem prudent to administer teicoplanin initially at least 12 mg/kg/day to burn patients and to monitor levels, with the expectation that higher doses will be required in patients with an elevated drug clearance. A target minimum trough serum concentration of 15 mg/L is recommended.

β-Lactams

The indications for using this group of agents is the same as that for using any broad-spectrum agent active against Gram-negative bacteria. The presence of MRSA in most units requires that they be combined with a glycopeptide in the empirical treatment of sepsis before identification of a pathogen.
Ticarcillin/clavulanate

Adam et al. studied the pharmacokinetics of both components (5.2 g in total, administered 2–3 times/day) in 15 burn patients, seven with burns ranging from 22–58% body surface area and eight with burns of 3–5%. No data on time of first administration after the burn or creatinine clearance were given. The results were compared with historical data from healthy controls.

Wide intra- and inter-individual variations were noted in the burn patient group. The volume of distribution and elimination half-life of both components were increased, but was much greater for clavulanate. The total clearance was also significantly increased for both components. In conclusion the authors note that, despite the increased terminal half-lives of ticarcillin and clavulanate, there was no evidence of accumulation, and in view of the serious nature of infection in burn patients, they recommended the highest dosage of the drug.

The mean serum concentration versus time plots are perhaps of more interest. Compared with normal individuals, the concentrations observed in burn patients were similar but reduced by approximately 0.6 log. Hence at 1 h, the mean concentration of ticarcillin in non-burn patients was 200 mg/L, whilst for burn patients it was 50 mg/L: at 5 h the concentrations were 20 mg/L and 4 mg/L, respectively. However, the concentrations in burn patients ranged from 10 to 200 mg/L at 1 h, from 1 to 50 mg/L at 4 h. Given these widely variable results, the dosing regimen used by these authors would appear too low, as some patients had subtherapeutic levels early in their course of therapy.

Ceftazidime

Walstad et al. studied the pharmacokinetics of ceftazidime in eight patients with burns. The surface area of the burns ranged from 20 to 80%. The mean creatinine clearance was 108 mL/min (range, 64–156 mL/min). Excluding one patient who was 21 days post-burn, the average time from burn injury to administration of ceftazidime was 3.5 days.

In burns patients, the pharmacokinetics of ceftazidime were significantly different compared with other patient groups although much interpatient variation was noted. The apparent volume of distribution was substantially increased, as was the elimination half-life. These changes will have consequences for the ceftazidime dosing regimen. Further studies are required to evaluate the changes in full. In another study, Rio et al. compared serum ceftazidime concentrations in healthy subjects and severe burn patients during continuous infusion. Each group was sub-divided to receive either 4 or 6 g/day of ceftazidime by infusion. Six burn patients were studied (three in each subgroup). Their creatinine clearances ranged from 85 to 142 mL/min, but time since the burn was not stated. Serum concentrations after either dosage in burns patients were 18–43% lower than in healthy subjects. The authors suggest that continuous infusion of 6 g/day ceftazidime may be most advantageous to treat serious infections in burn patients.

Carbapenems

The use of carbapenems in burns units has increased with the emergence of Acinetobacter spp. as pathogens in many units.

Imipenem. Boucher et al. studied the use of imipenem in 11 patients with burns ranging from 13 to 82% of body surface area. The time of administration of antibiotic ranged from 7 to 25 days post-burn, and the patients’ creatinine clearance from 17 to 218 mL/min/1.73 m². Overall, no pharmacokinetic parameter was significantly different from previously reported parameters in normal volunteers ($P > 0.005$). However, substantial interpatient variability was noted. For example, the terminal half-life in normal volunteers (mean ± s.d.) was 0.93 ± 0.09 h, whilst for burns patients it was 1.12 ± 0.44 h. Imipenem clearance was significantly related to creatinine clearance. In summary, they concluded that an adjustment in dosage or dose interval might be considered in those patients with burns who have an abnormally high or low creatinine clearance.

Meropenem. Clinical experience with meropenem in burns is limited, but a study in non-burn patients suggests that the pharmacokinetics are very similar to imipenem.

Yoshida et al. looked at the pharmacokinetics of meropenem in five patients, including two patients with burn infections. At a dosage of 1 g iv bd, serum concentrations at 1 h were in the order of 20–25 mg/L. No data on burn size, creatinine clearance, age of patients or time of the burn is given.

We have measured meropenem levels in one patient, a 13-year-old boy, weighing 50 kg. At a dose of 1 g every 8 h (60 mg/kg/day, i.e., 1.5 times the standard recommended maximum dose), the serum concentrations 1 h after administration was 8.8 mg/L and the trough level was <1 mg/L. These concentrations are much lower than expected in normal individuals.

Quinolones

Ciprofloxacin

Metz et al. studied five burn patients and compared the pharmacokinetics of ciprofloxacin with data from 12 healthy volunteers. The burned surface area ranged from 18 to 22% and treatment was started 3–5 days post-injury. Details of creatinine clearance were not given. Ciprofloxacin 200 mg was administered every 12 h as an iv infusion over 30 min. Single dose pharmacokinetics were
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measured after the first dose and repeated after 5 days of treatment. The total clearance of ciprofloxacin increased after multiple dosing in burn patients but decreased in the volunteer group. An increase in renal clearance accounted for the elevation in total clearance in the burned patients. Renal clearance for volunteers on day one and day five of therapy was 16 L/h and 14 L/h, respectively, whereas in the burn patients the figures were 17 L/h and 26.5 L/h, respectively. The authors concluded that the alteration in pharmacokinetics might not be sufficiently large to require an increase in dosage. Others have also studied the pharmacokinetics of iv ciprofloxacin in burn patients. In this study, the mean burn area was 35%, the mean creatinine clearance 126 mL/min (range, 74–168 mL/min) and the mean time following burn injury was 8 days (range, 4–12 days). In comparison with other patient groups, the mean ciprofloxacin clearance was greater (29.1 versus 17 L/h) and the mean elimination half-life reduced (4.5 versus 6.5 h). A large degree of variability in all pharmacokinetic parameters was noted, being as much as a nine-fold in some cases. A good correlation between ciprofloxacin clearance and creatinine clearance was noted (r = 0.85). This variability, they suggested, made it difficult to choose a standard dose with which to treat all patients.

Garrels et al. suggested that burn patients are good candidates for individualized dosing, as proposed by Forest et al. This group studied the pharmacokinetics of intravenous ciprofloxacin in 74 seriously ill non-burn patients who were treated with dosages ranging from 200 mg every 12 h to 400 mg every 8 h. Pharmacokinetic parameters were analysed in relation to clinical outcome, MIC and microbiological eradication of the infecting organism. A significant association was found between outcome and the area under the inhibitory time curve (AUIC). AUIC is the area under the concentration versus time curve for 24 h, divided by the MIC (AUC0–24/MIC), and is expressed in SIT units (inverse serum inhibitory titre integrated over time). An AUIC <125 SIT was predictive of clinical and microbiological failure (P = 0.002). The major variables in achieving an SIT of 125 were the MICs for the infecting organism and the variability of ciprofloxacin pharmacokinetics in individuals. They designed a dosing algorithm to achieve a SIT of 125 based upon the probable MIC for the infecting organism, patient creatinine clearance and bodyweight. When a range of MICs and creatinine clearance were substituted into the dosing algorithm, most of the dosing regimens for situations where the MIC was >0.25 mg/L required doses of ciprofloxacin in excess of 1200 mg/day in order to achieve an AUIC of >125 SIT. They also noted that their patient population had ciprofloxacin clearances only approximately half the values of age-matched volunteers in the literature. Thus, for a population with ciprofloxacin pharmacokinetics similar to those of volunteers, a maximum dose of 1200 mg/day is only likely to achieve an AUIC of >125 SIT for organisms with a MIC even lower than 0.25 mg/L.

For extremely sensitive organisms, therefore, ciprofloxacin dosing should not be a problem. The difficulty lies with organisms such as P. aeruginosa which often have MIC >0.5 mg/L. For organisms with an MIC of 0.25 mg/L, Forrest et al. suggested a dose of 1200 mg/day of ciprofloxacin. Whilst this was well tolerated by their patients, the maximum recommended dose in the data sheet is 800 mg/day. Organisms with an MIC of >0.25 mg/L, or patients with elevated rates of clearance would require a dose of >1200 mg/day. As an alternative to increasing the dose to >1200 mg/day, a second agent could be used in combination, and data show significant benefits from combining a ureidopenicillin with ciprofloxacin. What are the implications for burn patients? The Gram-negative microorganisms that cause infection in burns, e.g. P. aeruginosa and Acinetobacter spp., tend to have MICs in the range 0.1–1.0 mg/L and a proportion of burn patients will have high rates of drug clearance. Thus, the doses recommended by Forrest et al. may well be inadequate to achieve an SIT of 125 for organisms with an MIC >0.25 mg/L. It would seem prudent in some burn patients to use ciprofloxacin at a dose of at least 1200 mg/day and, possibly, in combination with another agent. Such high doses might not be necessary to treat very sensitive organisms or in patients with impaired drug clearance.

Summary

The prognosis for burn patients has increased significantly as a result of improvements in resuscitation, burn wound care, nutritional status, etc. Infection still remains the predominant determinant of wound healing, the incidence of complications and outcome. Antibiotics together with surgical intervention (where indicated) are the mainstay of treatment when sepsis occurs.

Profound physiological changes occur following a burn, which have a significant affect on drug handling. In 1976, Zaske et al. described the changes in aminoglycoside pharmacokinetics producing subtherapeutic concentrations, but despite this early report, a question mark remains over the adequacy of dosages of other classes of antibiotics.

There is a paucity of published work, both in terms of number of studies and number of patients enrolled within them, to support administration at standard dosage of many antibiotics in burn patients. This is perhaps to be expected with such a specialized area and restricted patient population. Even when pharmacokinetic studies have been done, however, because there is no standardization of the burn patient population, the results are of limited value. This may explain why some studies find an increased dosage requirement whilst others do not. Standardization of all the variables is not necessary, and probably impossible. Certain parameters, such as conducting the study either in the acute or the hypermetabolic phase, ensuring that enough patients with high creatinine clearance are
included and separating children from adults, need to be predefined, as their influence on studies may be critical.

Placing these criticisms aside, the consistent message for almost all studies is the extreme variation in drug handling between patients. Compared with a normal population, the burns patient population is much more diverse, with some patients whose excretion of an antibiotic may be significantly higher than that of the most rapid excreter in the normal population. Most studies also show that there is no single measurable factor that correlates with the changed pharmacokinetics, hence making it difficult, if not impossible, to predict the patients with enhanced drug handling who require dosage adjustments.

Future efficacy studies of antibiotics in burns patients must ensure that toxic levels do not occur but that therapeutic levels are achieved in every patient (or identify if this is not the case).

There is a legitimate concern that the second criterion has not been fulfilled for burn patients. The rapid clearance of antibiotics, even with drugs such as β-lactams, where dosage is often perceived as being sufficiently in excess of requirement, means that some patients may be exposed to subtherapeutic levels. Any reduction in antibiotic concentrations is likely to be more significant in burn patients as they are immunocompromized and often infected with Gram-negative pathogens such as P. aeruginosa or Acinetobacter spp., which have higher MICs compared with other Gram-negative species.

For drugs where levels are routinely monitored, i.e. the aminoglycosides and vancomycin, identification of subtherapeutic levels should not be a problem. The challenge has been to achieve therapeutic levels rapidly, as this improves outcome from sepsis. One answer, in the case of aminoglycosides, is to measure FD pharmacokinetics, and alter dosing appropriately.

For drugs where concentrations are not routinely measured, the clinician needs a means of identifying those patients with subtherapeutic antibiotic levels. The similarities of the systemic response to burn injury and infection make clinical assessment of response to treatment an unsuitable method. Furthermore, failure to respond to therapy may be due to a variety of other factors, and subtherapeutic levels may not be considered a likely reason for failure if an ‘appropriate’ dose is being administered. Ascertainment of antibiotic levels would therefore seem necessary in this group of patients, but the target antibiotic levels also need to be defined. For β-lactam agents, efficacy is related to time above the MIC. In non-immunocompromised patients, maintaining levels above the MIC for part of the dosing interval is usually sufficient as host defences help to combat the infection; however, burn patients are immunocompromised. An argument can be made for concentrations of β-lactams to be maintained above the MIC for longer, perhaps throughout the dosing period, in burn patients: continuous infusion may have a role to play.

How should the concern over subtherapeutic levels be addressed? The nature and the size of any problem could be established by measuring levels of every antibiotic. A multi-centre study would be required in order to enrol sufficient patients. Levels could be processed centrally, and whilst this may not be rapid enough for the individual patient, it would establish whether there is a significant problem with dosing. Should this prove to be the case, then the availability of HPLC facilities in more hospital laboratories could provide the means to measure rapidly antibiotic levels in the future.

In the meantime, one should ensure that patients receive the optimum dosage of antibiotic, according to current available data. Although there is no one readily measurable factor that will identify all patients with the need for increased dosage requirements, many studies have shown a degree of correlation with creatinine clearance. Burns patients with a normal or elevated creatinine clearance should be given at least the maximum recommended dose.

Acknowledgement

I would like to thank Mr J. A. Clarke, Consultant Burns and Plastic Surgeon, for his advice and comments.

References


