Pharmacokinetics of a single dose of teicoplanin in burn patients

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Patients with severe burns are susceptible to infection with Gram-positive organisms including methicillin-resistant Staphylococcus aureus, and often require higher antibiotic dosages compared with other patients. This study examined the pharmacokinetics of a single iv dose of teicoplanin (12 mg/kg) in 15 adults and five children with severe burns. Adults were aged 21–82 years with a median total body surface area (TBSA) burn of 30% (range 15–60%). Children were aged 10 months–10 years with median TBSA burn of 15% (10–30%). At 12 h, the median serum teicoplanin concentration was 12.8 mg/L (9.0–27.1 mg/L) in adults and 7.6 mg/L (6.6–10.8 mg/L) in children, (P < 0.01); at 24 h, the corresponding values were 8.3 mg/L (4.6–12.9 mg/L) and 5.2 mg/L (4.2–6.0 mg/L). Using a three-compartment model, the median terminal half life in adults was 114 h (47–278 h). Children fitted a two-compartment model with a terminal half-life of 38 h (21–41 h). The median concentration of teicoplanin in fluid from the burn wound was 60% of the serum antibiotic concentration. A single iv dose of 12 mg/kg of teicoplanin was sufficient to produce therapeutic serum concentrations in burn patients for 24 h, but monitoring of antibiotic levels in serum may be advisable in those with high total clearance, especially children.

Introduction

The pharmacokinetics of many antibiotics are altered in burn patients as a result of changes in renal function, cardiac output, serum protein binding, and plasma volume (Boucher, Kuhl & Hickerson, 1992), and loss of drug across the burn wound (Glew, Moellering & Burke, 1976). Patients with severe burns often require high doses of antibiotics to maintain therapeutic concentrations, and it is difficult to predict the required dosage from the drugs’ pharmacokinetics in other patients. Previous work in burn patients has shown that elimination half-life is decreased for gentamicin (Zaske et al., 1976), tobramycin (Loirat et al., 1978), amikacin (Zaske, Sawchuk & Strate, 1978), and vancomycin (Garrelts & Peterie, 1988); total clearance is increased for
vancomycin (Rybak et al., 1990), ciprofloxacin (Metz et al., 1989), ceftazidime (Walstad, Aanderud & Thurmann-Nielson, 1988), and ticarcillin (Adam et al., 1989), and the volumes of distribution of ceftazidime (Walstad et al., 1988) and ticarcillin (Adam et al., 1989) are increased.

Teicoplanin is a glycopeptide antibiotic active against most Gram-positive bacteria including methicillin-resistant Staphylococcus aureus (MRSA). Its use has increased because of its ease of administration, safety (Davey & Williams, 1991) and long serum half-life (Rowland, 1990). It is highly protein bound and eliminated almost entirely by renal mechanisms in healthy individuals (Rowland, 1990). Potel et al. (1990), using a single dose of 10 mg/kg of teicoplanin in adult burn patients, reported a mean serum half-life of 39–64 h, but only sampled for up to 96 h after administration. The elimination half-life was not significantly different from the controls, but serum concentrations fell below 8 mg/L at 12 h in 16 of 20 adults.

A study was performed in 15 adults and five children with severe burns to determine the serum concentrations after a single dose of 12 mg/kg of teicoplanin. Sampling was continued until the lower limit of detection was reached in order to accurately determine the terminal half-life. The concentration of teicoplanin in burn wound fluid was also measured.

Methods

Adults with burns over 15% total body surface area (TBSA) and children (>2 months) with burns over 10% TBSA were eligible for inclusion. Patients who had received systemic antibiotics within the previous 48 h, with the exception of flucloxacillin prophylaxis in children (a protocol in use at the time of the study), pregnant or nursing mothers, patients with only inhalation burns, children with only superficial scalds, and those with significant renal or hepatic impairment, were excluded. Patients in whom therapy for concurrent infection was started after administration of teicoplanin were not withdrawn. The study was approved by the hospital ethics committee and informed consent was obtained.

Teicoplanin 12 mg/kg was given as a bolus iv dose. The antibiotic was supplied by Marion Merrell Dow (Winnersh, Berks) as a powder for reconstitution, and made up to a concentration of 100 mg/mL with sterile water for injection. Blood was drawn immediately prior to administration of the teicoplanin, at 5, 10, 15, 20 and 30 min, and 1, 2, 3, 4, 6, 8, 12, 24 h, 2, 3, 4 and 5 days; thereafter samples were taken every 2–3 days or until serum concentrations fell below the limit of detection, up to a maximum of three weeks.

Patient samples were stored at 4°C until separation of the serum by centrifugation and then at −70°C until assayed. Teicoplanin concentrations were determined by an agar diffusion method (Patton et al., 1987), using Bacillus subtilis (NCTC 10400, ATCC 6633, (Difco, Michigan, USA) as indicator organism. In the presence of β-lactam antibiotics, samples were treated with β-lactamase (Genzyme Biochemicals, Suffolk). One of three multi-resistant S. aureus strains (clinical isolates) was employed as indicator organism when antibiotics other than β-lactams were given concomitantly with teicoplanin. The limit of sensitivity using B. subtilis was 0.5 mg/L and using S. aureus was 1.0 mg/L. The coefficients of variation at the high (40 mg/L), median (8 mg/L) and lower end (1 mg/L) of sensitivity were 5.38%, 5.84% and 7.82%, respectively.
To determine wound exudate antibiotic concentrations, paper safety filters (normally used in glass pipettes) (Anachem, Luton, UK) were placed on the burn wound and left in place until wet. Blood-contaminated fluid was avoided so as not to give falsely high concentrations. Fluid was removed from the filters by compression in a sterile syringe and the antibiotic assay performed as above. Good recovery of teicoplanin from the pipette filters was achieved, using known concentrations of teicoplanin (data not shown).

Statistical methods
Where possible, plasma teicoplanin concentrations were modelled using a triexponential decay in accordance with earlier studies (Verbist et al., 1984; Potel et al., 1990) according to the equation:

$$C_p(t) = Pe^{-\alpha t} + Ae^{-\beta t} + Be^{-\gamma t},$$

where $C_p(t)$ is the concentration in plasma at time $t$; $\alpha$, $\beta$, and $\gamma$ are the three exponential coefficients during the three phases. The area under the plasma concentration time curve ($\text{AUC}_{0-\infty}$) was extrapolated to infinity using $C_p/\gamma$ for the last sample time. The clearance, $Cl$, was determined by $Cl = \text{dose}/\text{AUC}$ assuming a bioavailability of 100%. The half-life for each phase was determined from the individual rate constants. A two compartment model was used to describe the data where there were only 2–3 points on the terminal phase or when the patient died before 72 h. Similarly, for the children, samples taken more than 96 h after antibiotic administration were close to the limit of sensitivity of the assay and the terminal elimination rate constant would have been calculated using only two points if a three compartment model had been used. A non-linear regression program MW/Pharm version 3.03 (Kinfit) (MEDI/WARE B.V. Groningen, Netherlands) was used to analyse the data.

Differences between non-parametric variables were determined by the Mann-Whitney test (Armitage & Berry, 1987a) and stepwise multiple regression was performed to determine relationship between serum teicoplanin concentrations and the size of the burn or other patient factors (Armitage & Berry, 1987b), using Minitab version 8.21 (Clecom, Edgbaston, UK).

Results
The characteristics of the study population are shown in Table I. The median TBSA burn was greater in adults than in children, but the difference was not statistically significant. Of the 15 adults under study, three died of their injuries before completion of sampling (on days 1, 3 and 8), and a fourth patient was started on regular teicoplanin treatment on day 6 and no further samples were collected.

Teicoplanin was administered within 48 h of admission, ie. during fluid resuscitation,

<table>
<thead>
<tr>
<th></th>
<th>adults ($n = 15$)</th>
<th>children ($n = 5$)</th>
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<tbody>
<tr>
<td>Number of males</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Median total body surface area of burn (range)</td>
<td>30 (15–60%)</td>
<td>15 (10–30%)</td>
</tr>
<tr>
<td>Mean age, years (range)</td>
<td>44 (21–82)</td>
<td>5 (10 mth–10)</td>
</tr>
<tr>
<td>Mean weight, kg (range)</td>
<td>72 (50–104)</td>
<td>22 (10–39)</td>
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in 12 of 15 adults and two of five children. Two excisions (one child and one adult) and one escharotomy (adult) were performed within this 48 h period. Of the remaining six patients, two adults and two children were given teicoplanin before excision and one adult and one child were given teicoplanin prior to change of dressings, after fluid resuscitation was complete.

Six hours after the dose, the median serum concentration was 18.4 mg/L (range 11.4–28.1 mg/L) in adults and 15.5 mg/L (range 11.6–19.1 mg/L) in children (no significant difference). At 12 h, the median serum concentration was 12.8 mg/L (9.0–27.1 mg/L) in adults and 7.6 mg/L (6.6–10.8 mg/L) in children (95% confidence interval (CI) for difference 2.0–6.2, $P < 0.01$), and at 24 h the corresponding values were 8.3 mg/L (4.6–12.9 mg/L) and 5.2 mg/L (4.2–6 mg/L) (95% CI for difference 0.8–5.6, $P < 0.05$) (Figures 1 and 2). Clearance per kg body weight was significantly greater in children than in adults (median 0.018 L/h.kg vs. 0.012 L/g.kg, 95% CI for difference 0.003–0.013, $P = 0.009$).

It was possible to fit the serum antibiotic concentrations to a three compartment model in 11 of the 15 adults, giving a median terminal half life of 114 h (range 47–278 h) (Table II). A two compartment model had to be used for the other four adults in whom the $\beta$ phase half-life was 10–32 h (median 26 h). In Figure 3, the serum concentrations of all 15 adults are shown. In the 5 children, the median $\beta$ phase half-life was 38 h (range 22–41 h) (Figure 4, Table II).

No significant correlation was found between age, TBSA burn, or serum creatinine concentration and teicoplanin concentrations at 12 or 24 h in adults. There was a significant negative correlation between serum total protein concentration ($x$) and serum teicoplanin concentration ($y$) at 12 h in adults $y[\text{mg/L}] = 36.2–0.404x$ (g/l), $F$ 9.06, $R^2$ (adj) = 40%, $P = 0.012$), but not at 24 h. Regression analysis was not performed on the data from the small number of children.
Teicoplanin pharmacokinetics

Figure 2. Serum teicoplanin concentrations in five child burn patients in first 24 h after an iv dose of 12 mg/kg.

Burn wound fluid was collected on 11 occasions from seven patients at times between 5.2 h and 72 h after teicoplanin was given. Two other patients had cetrimide or silver sulphadiazine on the burn wound which interfered with the bioassay and so were excluded; there was insufficient sample to perform the assay from another three patients, and the remaining patients were dressed following excision and grafting and therefore samples could not be obtained. The median concentration of teicoplanin in burn wound fluid between 5–72 h after the dose in seven patients was 0.6 times the serum concentration (range 0.2–1.3). In one patient teicoplanin was not detected at 6 h after administration (concentration < 1.0 mg/L). No other burn fluid samples were collected from this patient (Table III).

Table II. Pharmacokinetic parameters for 20 patients after a single iv dose of teicoplanin 12 mg/kg. Medians and ranges are given (\(T_1\), \(T_2\), \(T_3\); half-lives of distribution and elimination phases; \(AUC_{\infty}\), area under plasma concentration curve; \(Cl\) clearance per kg body weight; \(V_{\infty}\), apparent volume of distribution per kg of body weight at the steady state; MRT mean residence time)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Adults three-compartment (n = 11)</th>
<th>Adults two-compartment (n = 4)</th>
<th>Children two-compartment (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(T_1), h</td>
<td>0.40 (0.10–0.65)</td>
<td>0.64 (0.52–0.75)</td>
<td>1.04 (0.65–1.9)</td>
</tr>
<tr>
<td>(T_2), h</td>
<td>6.6 (2.4–16.2)</td>
<td>26 (10–32)</td>
<td>38 (22–41)</td>
</tr>
<tr>
<td>(T_3), h</td>
<td>114 (47–278)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>(AUC_{\infty}), h.mg/L</td>
<td>1173 (703–3090)</td>
<td>843 (707–1071)</td>
<td>666 (422–843)</td>
</tr>
<tr>
<td>(Cl), L/h.kg</td>
<td>0.010 (0.004–0.017)</td>
<td>0.015 (0.011–0.018)</td>
<td>0.018 (0.014–0.029)</td>
</tr>
<tr>
<td>(V_{\infty}), L/kg</td>
<td>1.0 (0.59–2.0)</td>
<td>0.45 (0.20–0.52)</td>
<td>0.69 (0.62–0.82)</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>91 (44–296)</td>
<td>31 (12–41)</td>
<td>41 (24–50)</td>
</tr>
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</table>

*Two adult patients died within 72 h of antibiotic administration.
Discussion

All but two patients received the teicoplanin either within 48 h of admission or immediately prior to excision and grafting of the burn wound or both, at times when maximum cutaneous fluid or blood loss would be expected. Nevertheless, a serum concentration of teicoplanin > 4 mg/L was maintained for 24 h after a single iv dose of 12 mg/kg in all patients. Ninety per cent of strains of S. aureus are inhibited at teicoplanin concentrations between 0.2–3.1 mg/L (Campoli-Richards, Brogden & Faulds, 1990). The mean serum concentration in adults of 8.3 mg/L at 24 h was nearly twice that reported by Potel et al. (1990) who used a dose of 10 mg/kg. A dose of
12 mg/kg has been used as prophylaxis during coronary artery surgery and gave a similar serum concentration of 7 mg/L at 24 h (Wilson et al., 1989).

In normal subjects, the pharmacokinetics are usually best described by a three compartment model, the half-life during the first and second phases being 20–30 min and 1.6–4 h, respectively (Rowland, 1990). The apparent terminal half-life in normal subjects varies between studies depending on the duration of sampling undertaken. Carver et al. (1989) suggest that discontinuation of sampling before 11 days post-dose will include distributional phase data in the terminal phase, thereby shortening the apparent terminal half-life. In our study, samples were collected until the serum concentration of teicoplanin fell below the limit of detection for the assay being used, and a median half-life of 114 h was obtained. Teicoplanin was detected in the serum for up to 22 days in adults and 8 days in children. In normal subjects with long duration of sampling (35 days), the terminal half-life after single dose teicoplanin is 130 h (Carver et al., 1989). The shorter half-life reported by Potel et al. (1990) may have been the result of their shorter sampling period. The median terminal half-life was shorter in some of our burn patients despite prolonged sampling, particularly in the children. The volume of distribution and clearance of teicoplanin found in the burn patients was similar to that in normal subjects (0.5–1 L/kg and 0.006–0.016 L/h/kg, respectively) (Rowland, 1990). However, clearance per kg body weight was significantly higher in children than adults, as anticipated from the results of previous studies in children (Bassetti & Cruciani, 1990).

In common with other antibiotic studies in burn patients, there was considerable variation between individuals. Differences in glomerular filtration rate do not always account for these differences. The serum half-life of aminoglycosides varies widely in burn patients even when serum creatinine or creatinine clearance are used to modify
the dosage regimen (Zaske et al., 1991). Size and frequency of dosing both need to be increased for vancomycin in burn patients to prevent prolonged periods of subinhibitory levels, despite normal creatinine clearance (Garrelts & Peterie, 1988).

Some of the apparent variation in the serum concentration of teicoplanin at 12 h in adults was explicable in terms of the serum total protein concentration. However, there was no significant correlation with serum creatinine or TBSA burns. Teicoplanin is highly protein bound (Rowland, 1990) and it is likely that the results of the microbiological assay were affected by the proportion of free teicoplanin in the serum.

Burn wound fluid collected from seven patients during this investigation was found to contain teicoplanin, indicating that at least some teicoplanin is lost through the burn in most patients. Good penetration of antibiotic through the burn, however, may be regarded as an advantage in the treatment of invasive burn wound infection. Rio et al. (1987) examined multiple dose pharmacokinetics in a study of 20 adult burn patients treated at a dosage of 5–14 mg/kg/day. The mean trough serum concentration was 7.4 mg/L and levels in burn tissue were a mean of 1.6 times greater. Results from our study indicate that the concentration of teicoplanin in fluid from the burn wound probably remains above 5 mg/L for at least 8 h. However, one patient had no teicoplanin detected.

In conclusion, a single iv dose of teicoplanin 12 mg/kg was sufficient to produce adequate serum concentrations for 24 h in all the burn patients studied, but elimination of antibiotic was more rapid in children than in adults. Serum monitoring may be advisable in children and others with high total clearance.

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References


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