Pharmacokinetic studies of linezolid and teicoplanin in the critically ill

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Objectives: To determine the pharmacokinetic characteristics of linezolid and teicoplanin in critically ill patients.

Patients and methods: Serum was collected frequently during day 0 and then pre- and 1 h post-dose on days 1, 2, 3, 5, 7 and every third day thereafter during treatment. Serum linezolid concentrations were analysed using HPLC. Serum teicoplanin levels were analysed by fluorescence polarization immunoassay.

Results: A two-compartment model was required to characterize linezolid pharmacokinetics (n = 28) and account for the accumulation seen after multiple dosing. The estimated clearance was 0.049 ± 0.016 L/h/kg (± S.E.M. of estimate). At steady state (dosing interval 12 h), linezolid serum concentrations exceeded the breakpoint of 4 mg/L for 10.88 h (95% CI 10.09–11.66) after a 600 mg dose with an AUC/MIC of 92.4 (95% CI 57.2–127.7). Teicoplanin was best described by a two-compartment model (n = 26). The clearance was 4.97 ± 1.58 L/h. Serum levels exceeded the breakpoint of 4 mg/L for the entire dosing interval in all subjects (400 mg dose every 12 h) with an AUC/MIC of 399.3 (95% CI 329.6–469.0). However, only four of 14 exceeded trough serum concentrations of 10 mg/L. For both agents, trough levels were similar in those who survived and those who died.

Conclusions: Linezolid dosage at 600 mg every 12 h was adequate in the critically ill without need for adjustment for renal function. For teicoplanin, further study is needed to confirm if a trough of 10 mg/L is associated with a higher rate of cure than 5 mg/L. If so, serum drug assays would be needed to ensure a therapeutic level.

Keywords: critical care, pharmacokinetics, AUC, HPLC

Introduction

Linezolid is the only commercially available oxazolidinone, the first new class of antibiotic developed in the last three decades. It binds to the 50S subunit on the bacterial ribosome producing an early inhibition of protein synthesis.¹² Linezolid is predominantly bacteriostatic but has good activity against Gram-positive organisms including methicillin-susceptible Staphylococcus aureus (MSSA) and methicillin-resistant S. aureus (MRSA), coagulase-negative staphylococci (CoNS) and vancomycin-resistant enterococci (VRE).³

As yet, there is only one report of the pharmacokinetics of linezolid in critically ill populations—based on intensive care unit (ICU) patients recruited to the compassionate use...
programme. The pharmacokinetic profile of linezolid has also been studied in a wide variety of subjects including normal volunteers, children, in patients with multiresistant Gram-positive infections, or community-acquired infections taking oral doses and in patients undergoing chronic renal replacement or peritoneal dialysis. Linezolid has a bioavailability of 100% when taken orally, is highly water-soluble and has good tissue penetration. It is excreted through both the renal and biliary systems in approximately equal proportions.

Although excretion by several mechanisms may be desirable in a drug used in the critically ill, drug distribution and excretion are frequently altered in such patients and specific characterization of the pharmacology of a compound is necessary to ensure appropriate dosing. Renal impairment is common, with a reported incidence as high as 40%. Increased capillary leak, decreased plasma proteins and aggressive fluid resuscitation may alter the volume of distribution.

Teicoplanin, a glycopeptide, is a standard antibiotic for the treatment of hospital-acquired Gram-positive infections. It has a spectrum of activity similar to linezolid and is almost entirely excreted renal. The dose of teicoplanin must be reduced in the presence of reduced glomerular filtration. In healthy subjects, teicoplanin disposition is best modelled by tri-phasic elimination. However, its pharmacokinetic profile has not been extensively studied in ICU patients.

Both linezolid and teicoplanin have good activity against S. aureus strains isolated in the British Isles, with all bacteremic strains being susceptible. In contrast, CoNS have a wide range of susceptibility. Of strains isolated from bacteremic patients, 23% of oxacillin-susceptible organisms and 34.8% of oxacillin-resistant organisms are resistant to teicoplanin. For Enterococcus faecalis isolated from bacteremic patients, 2.7% are resistant to teicoplanin and none to linezolid, whereas equivalent figures for Enterococcus faecium are 15.2% and 0%, respectively.

Maintenance of antibiotic concentrations within a therapeutic range is of particular importance in the critically ill. The area under the curve of the concentration–time graph is vital to ensure adequate tissue penetration and bacterial inhibitory concentrations. The BSAC susceptibility breakpoint for both linezolid and teicoplanin is 4 mg/L (S ≤ 4 mg/L, R > 4 mg/L). Time above MIC (or area-under-curve to MIC ratio) for free drug concentrations is an important pharmacodynamic parameter, correlating with efficacy in glycopeptides and linezolid. In animal and human studies, AUC/MIC ratios are predictive of favourable outcomes.

We recently conducted a randomized, double-blind, prospective study comparing linezolid against teicoplanin in the treatment of suspected or proven Gram-positive infections in critically ill patients in two mixed medical–surgical, tertiary referral ICUs. As part of this trial, a protocol was also drawn up to allow study of the pharmacokinetic profile of those two drugs.

Methods

A randomized, double-blind, double-dummy trial was performed during June 2000–December 2001 on the two ICUs of University College London and the Royal Free Hospitals using separate randomization schedules. Patients with sequential randomization numbers were also recruited to the pharmacokinetic study.

Approval was obtained from the Ethics Committees of both hospitals involved, and the conduct of the study was consistent with Good Clinical Practice guidelines. Before inclusion in the trial, comprehensive information regarding the trial objectives and procedures were provided to the patient or their next of kin. Agreement to participate (if unsedated and mentally competent) was obtained from the patient; otherwise agreement was sought from the next of kin.

Patients in either ICU with known or suspected Gram-positive infection were recruited. Infection caused by MSSA and MRSA, enterococci (including VRE), and CoNS were all eligible. Patients were enrolled if they had at least two of the following: (i) fever (body temperature 38°C orally or 39.5°C rectally, or hypothermia (body temperature ≤35.5°C taken rectally); (ii) respiratory rate >30 breaths per min; (iii) systolic hypertension (systolic blood pressure <90 mm Hg); (iv) heart rate >120 bpm; (v) PaO₂ < 8kPa (60 torr) on air or PaCO₂ of >6.3 kPa (47 torr) on air; (vi) requirement of mechanical ventilation; (vii) elevated peripheral white cell count (WBC) >10000 cells/mm³, >15% immature neutrophils regardless of total peripheral WBC, leukopenia with total WBC <4500 cells/mm³.

Treatment schedule

Patients were randomized to receive intravenous dosing of either: (i) active linezolid (600 mg, 12 hourly) plus teicoplanin dummy (one dose given 12 hourly for three doses, then one dose 24 hourly); or (ii) active teicoplanin (400 mg 12 hourly for three doses, then 400 mg 24 hourly) plus linezolid dummy (one dose 12 hourly).

The placebo dummies were prepared by the local pharmacies of both hospitals and were identical in appearance to the active antibiotic. Investigators and patients were blinded to the active agent used. These were administered sequentially either one first, over 30 min through a standard intravenous infusion giving-set. The total infusion duration was therefore 1 h. The post-dose serum samples described below were taken immediately following the end of administration of the second bag.

Teicoplanin (or teicoplanin dummy) dosage was modified in renal failure. When the creatinine clearance—as estimated by the Cockcroft–Gault equation—was 400 mg dose was given every 72 h following the three loading doses given 12 h apart. A dose interval of 48 h was used for mild renal impairment.

All other routine ICU treatments were continued. The patients were excluded from other invasive studies. Other than the potential risk of interaction of linezolid with monoamine-type drugs, neither linezolid nor teicoplanin has known major drug interactions.

Blood was drawn upon initiation of therapy (at times 0, 15, 30, 45, 60, 75, 90, 135, 150 min then at 4, 6, 12 h), and then pre- and at 1 h post-dose on days 1, 2, 3, 5, 7 and every third day thereafter if needed. The four samples drawn early in the protocol allowed the blinded treatments to be given sequentially. These provided extra data points if the active drug was given first or baseline points if the drug was given second. Sampling continued for 300 h after the first dose if the patient was alive and in hospital. The samples were centrifuged at 1500 rpm for 5 min and the serum decanted and kept at −70°C until sent for analysis.

Serum creatinine was measured at daily intervals; by applying the estimated creatinine clearance was estimated using the Cockcroft–Gault equation:

\[
\text{Estimated creatinine clearance} = \frac{[140 – \text{age}] \times \text{weight}}{[\text{Cr}] \times 0.81}
\]

where a gender correction factor of 0.85 was applied for females; patient weight units are kilograms; [Cr] = serum creatinine measured in μmol/L; and creatinine clearance has units of mL/min.
Pharmacokinetics of linezolid and teicoplanin in the critically ill

Linezolid assay
High performance liquid chromatography was used to measure the serum linezolid level. The stationary phase was Hypersil 5ODS, 10 cm × 4.6 mm (Waters Corporation, Milford, USA). The mobile phase was 1% ortho-phosphoric acid, 30% methanol, 2 g/L heptane sulphinic acid, adjusted to pH 5 by the addition of 10 M sodium hydroxide. The pump flow rate was 1.0 mL/min. UV absorbance detection was used (maximum absorbance wavelength 254 nm). A Gina 50 autosampler was used ( Dionex, Macclesfield, UK) and the integrator was a Trilab 2000 (Trivector, Bedfordshire, UK).

Sample were prepared by mixing aliquots (50:50) of the specimen with acetonitrile. The samples were allowed to rest at ambient temperature for 10 min and centrifuged at 5000 g for 5 min. Twenty μL of the supernatant was injected. The retention time of linezolid was ~ 6 min. The intra- and inter-day variability (standard deviation/mean × 100) was < 8% for serum samples containing 2.5, 8 and 18 mg/L linezolid (limit of quantitation 0.1 mg/L).

Teicoplanin assay
Teicoplanin was quantified by fluorescence polarization immunoassay (Opus Diagnostics Inc., Fort Lear, NJ, USA). The intra-day variability (standard deviation/mean × 100) was < 5% and the inter-day variability < 7.5% for samples containing 8, 36 and 76 μg/L teicoplanin (limit of quantification 1 μg/L).

Data analysis
The population pharmacokinetic models for linezolid and teicoplanin were developed using a population approach implemented in the NONMEM program, version V level 1.1 using the first order (FO) estimation method.

Various structural pharmacokinetic models were tried. A one-compartment model following administration by intravenous infus ion accurately described the plasma concentration-time profile of linezolid following the first dose, whereas a two-compartment model was necessary to account for the accumulation following subsequent doses, for both linezolid and teicoplanin. Random effects were also implemented on the pharmacokinetic parameters, clearance (CL) and volume of distribution (V). In each case it was assumed that the variable was log-normally distributed. A combined additive and multiplicative model for intra-subject residual variability was used for linezolid, whereas a multiplicative model was used for teicoplanin.

The ability of a number of available covariates, including weight, height, age, sex, renal function and presence or absence of renal replacement therapy, inter-subject variability in CL and V, was evaluated using likelihood ratio tests. Goodness of fit was additionally assessed by visual inspection of residual plots including observed value versus predicted value, residual versus time and predicted value; and weighted residual versus time and predicted value.

Monte Carlo simulations were performed using the linezolid AUC distributions derived from the patients for whom AUC values were calculated. MIC values for S. aureus, CoNS and Enteroococcus spp. were obtained from the BSAC bacteremia resistance surveillance programme. From earlier studies, the major parameter in determining efficacy of linezolid was the AUC/MIC ratio with a pharmacodynamic target value of 100. The target ascertainment was determined for each MIC value in the distribution (Crystal Ball 2002; Decisioneering Inc., Denver, CO, USA). Target ascertainment rates were then calculated for each species using the MIC distribution data. Differences in non-parametric values were tested by Mann–Whitney.

Linezolid concentrations peaked at 30 min after the first dose at 14.0 mg/L (s.d. 4.5 mg/L) falling to a trough of 1.4 mg/L (s.d. 1.1 mg/L) at 12 h. The trough was 2.8 mg/L (s.d. 2.7 mg/L) at 24 h, 3.9 mg/L (s.d. 4.4 mg/L) at 48 h and 4.5 mg/L (s.d. 6.2 mg/L) at 72 h. The plasma concentrations following the first dose of linezolid were initially modelled using a total of 196 sampling points. Although there was some under-prediction of peak concentrations, a one-compartment model gave an adequate fit to the data, which probably reflects the need for a more complicated model. Although a two-compartment model was not supported by the single-dose data, as described below, subsequently a two-compartment model was fitted to the multiple-dose data. A plot of the first dose data is shown in Figure 1.

The accumulation observed following the second and subsequent doses was poorly predicted from the individual parameter estimates obtained from the first dose and consequently a two-compartment model was fitted to the complete data set (399 concentrations). Comparison of predicted versus observed concentrations showed a reasonable fit to the data (r = 0.799) and the accumulation in a representative subject is shown in Figure 2. The predicted concentrations are individual estimates obtained with the POSTHOC option in NONMEM. The fit was repeated with the FOCE option in NONMEM but failed to converge. A FOCE fit was obtained with the single dose data and the parameter estimates were very similar to those obtained with the FO method.

There was a significant, positive correlation between clearance, initial volume of distribution and patient weight (Figure 3). Consequently in the final NONMEM model, clearance and initial volume of distribution were made proportional.
to body weight and this produced a significant improvement in the fit over the base model (judged by the decrease in the NONMEM objective function; 25.4). None of the other covariates contributed significantly to the fit. In particular, the five patients undergoing renal replacement therapy in the first 24 h did not show a difference in clearance compared with other patients. A formal test, in which renal replacement therapy was implemented as a covariate, confirmed the lack of difference in these patients. Table 1 lists the final parameter estimates. For a 70 kg individual the half-lives associated with the two-compartment model would be 2.59 h and 77.5 h. For all patients, clearance of linezolid was between 20 and 179 mL/min without renal support (20 patients) and between 31 and 91 mL/min with renal support (eight patients).

At steady state (dosing interval 12 h), linezolid serum concentrations exceeded the breakpoint of 4 mg/L for 10.88 h (95% CI 10.09–11.66) after a 600 mg dose with an AUC/MIC of 92.4 (95% CI 57.2–127.7). At the end of treatment, 24 patients were alive (16 cured, four improved, one failed, three indeterminate) and four died (one cured, one failed, two indeterminate). Trough levels at 24, 48 and 72 h were similar in those who survived (mean 1.9–2.9 mg/L) and those who died (mean 2.4–4.9 mg/L) (Mann–Whitney, NS) with one exception (11.3–24.8 mg/L). Trough concentrations were also similar in those who were

Table 1. Parameter estimates for the fit of a two-compartment model to linezolid concentration–time data using all the data of the dosage regimen

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>Standard error of estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL = $\theta_1 \times$ weight</td>
<td>0.0487 L/h/kg</td>
<td>0.0158 L/h/kg</td>
</tr>
<tr>
<td>$V_1 = \theta_2 \times$ weight</td>
<td>0.634 L/kg</td>
<td>0.039 L/kg</td>
</tr>
<tr>
<td>CLd</td>
<td>7.48 L/h</td>
<td>1.96 L/h</td>
</tr>
<tr>
<td>$V_2$</td>
<td>240 L</td>
<td>92.4 L</td>
</tr>
<tr>
<td>Time of infusion</td>
<td>0.5 h</td>
<td>Fixed</td>
</tr>
<tr>
<td>Inter-individual variability in CL</td>
<td>48.1%</td>
<td>51.5%</td>
</tr>
<tr>
<td>Inter-individual variability in $V_1$</td>
<td>22.4%</td>
<td>45.4%</td>
</tr>
<tr>
<td>Inter-individual variability in CLd</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Inter-individual variability in $V_2$</td>
<td>146%</td>
<td>74.6</td>
</tr>
<tr>
<td>Inter-individual variability in duration of infusion</td>
<td>80.1%</td>
<td>42.2%</td>
</tr>
<tr>
<td>Residual variability</td>
<td>19.0%</td>
<td>44.8%</td>
</tr>
<tr>
<td>proportional</td>
<td>2.34 mg/L</td>
<td>1.76 mg/L</td>
</tr>
<tr>
<td>additive</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CL, clearance; $V_1$, volume of compartment 1; $V_2$, volume of compartment 2; CLd, distributional clearance.

*No estimate available.
cured (mean 1.3–2.4 mg/L) and those who failed (mean 2.8–5.5 mg/L) (Mann–Whitney, NS).

Monte Carlo simulations indicated a target ascertainment for an AUC/MIC value of 100 of 76% for *S. aureus*, 95.8% for CoNS, and 75.4% for *Enterococcus* spp. Using the relative frequencies of these pathogens isolated from the patients in the study, the predicted clinical/bacteriological success rate for linezolid was 80.4%.

**Teicoplanin**

Teicoplanin concentrations peaked at 30 min after the first dose (33.4 mg/L s.d. 20.1 mg/L) falling to a trough of 4.2 mg/L (s.d. 5.0 mg/L) at 12 h. The trough was 6.6 mg/L (s.d. 3.7 mg/L) at 24 h, 7.4 mg/L (s.d. 3.1 mg/L) at 48 h and 8.9 mg/L (s.d. 3.7 mg/L) at 72 h. Teicoplanin was detectable up to 300 h after the last dose. The same strategy used for linezolid was applied to teicoplanin. In the first instance, only the data from the first dose were modelled (128 observations). A two-compartment model gave a good fit ($r=0.963$) to the data, and a representative subject shown in Figure 4. Parameter estimates are given in Table 2. None of the available covariates contributed significantly to the fit. Furthermore, the model significantly under-predicted the data beyond the first dose. As it was suspected that the terminal half-life was not well characterized in the 12 h following the first dose, data from all of the doses were fitted next.

The fit to all the data (374 observations; shown in Figure 5) was reasonable, if somewhat poorer than that obtained when only data from the first dose were modelled. However, the parameter estimates, as shown in Table 3, are more comparable to the values expected from the literature. The two half-lives generated from the two-compartment model were 3.12 h and 124 h. A three-compartment model was not supported by the data. Once more, none of the covariates helped to explain the variability in the data. At a dose interval of 24 h in patients treated for at least 48 h, trough serum concentrations exceeded 10 mg/L in only four of 14 individuals. Concentrations exceeded the MIC of 4 mg/L for the entire dosing interval in all subjects (400 mg dose every 12 h) with an AUC/MIC of 399.3 (95% CI 329.6–469.0).

### Table 2. Parameter estimates for the fit of a two-compartment model to teicoplanin concentration–time data following the first dose of the dosage regimen

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>Standard error of estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL</td>
<td>4.97 L/h</td>
<td>1.58 L/h</td>
</tr>
<tr>
<td>V1</td>
<td>9.84 L</td>
<td>4.29 L</td>
</tr>
<tr>
<td>CLd</td>
<td>8.31 L/h</td>
<td>1.68 L/h</td>
</tr>
<tr>
<td>V2</td>
<td>28.0 L</td>
<td>14.0 L</td>
</tr>
<tr>
<td>Time of infusion</td>
<td>0.5 h</td>
<td>Fixed</td>
</tr>
<tr>
<td>Inter-individual variability in CL</td>
<td>69.3%</td>
<td>14.3%</td>
</tr>
<tr>
<td>Inter-individual variability in V1</td>
<td>64.7%</td>
<td>50.8%</td>
</tr>
<tr>
<td>Inter-individual variability in CLd</td>
<td>49.0%</td>
<td>52.9%</td>
</tr>
<tr>
<td>Inter-individual variability in V2</td>
<td>88.3%</td>
<td>191%</td>
</tr>
<tr>
<td>Inter-individual variability in duration of infusion</td>
<td>70.6%</td>
<td>88.1%</td>
</tr>
<tr>
<td>Residual variability</td>
<td>17.2%</td>
<td>74.0%</td>
</tr>
</tbody>
</table>

CL, clearance; V1, volume of compartment 1; V2, volume of compartment 2; CLd, distributional clearance.

### Table 3. Parameter estimates for the fit of a two-compartment model to teicoplanin concentration–time data using all the data of the dosage regimen

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>Standard error of estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL</td>
<td>0.689 L/h</td>
<td>0.563 L/h</td>
</tr>
<tr>
<td>V1</td>
<td>25.3 L</td>
<td>4.29 L</td>
</tr>
<tr>
<td>CLd</td>
<td>3.93 L/h</td>
<td>3.19 L/h</td>
</tr>
<tr>
<td>V2</td>
<td>86.5 L</td>
<td>3.49 L</td>
</tr>
<tr>
<td>Time of infusion</td>
<td>0.5 h</td>
<td>Fixed</td>
</tr>
<tr>
<td>Inter-individual variability in CL</td>
<td>67.3%</td>
<td>143%</td>
</tr>
<tr>
<td>Inter-individual variability in V1</td>
<td>31.0%</td>
<td>110%</td>
</tr>
<tr>
<td>Inter-individual variability in CLd</td>
<td>95.0%</td>
<td>76.3%</td>
</tr>
<tr>
<td>Inter-individual variability in V2</td>
<td>71.4%</td>
<td>36.1%</td>
</tr>
<tr>
<td>Inter-individual variability in duration of infusion</td>
<td>288%</td>
<td>36.9%</td>
</tr>
<tr>
<td>Residual variability</td>
<td>43.8%</td>
<td>22.8%</td>
</tr>
</tbody>
</table>

CL, clearance; V1, volume of compartment 1; V2, volume of compartment 2; CLd, distributional clearance.
There was a noticeable positive correlation between CL and creatinine CL (CL\textsubscript{CR}), as shown in Figure 6, but a formal relationship between the two variables was not supported by a likelihood ratio test. The correlation coefficient between CL and CL\textsubscript{CR} was 0.366 (P = 0.066). In renal failure, the dose interval was increased to 48 or 72 h. The trough serum levels at least 48 h from the start of treatment were similar in those patients with creatinine clearance below 40 mL/min as those with a normal clearance, irrespective of the use of haemofiltration. Five of nine had trough levels < 10 mg/L. For three patients having haemofiltration over 48 h, trough levels were a median 7.7 mg/L (range 4.8–11 mg/L).

At the end of treatment, 19 patients were alive (14 cured, two failed, two improved, one indeterminate) and seven were dead (four failed, three indeterminate). Average trough concentrations at 24, 48 and 72 h were not significantly different between those who survived (6.2–8.4 mg/L) than those who died (8.3–10.3 mg/L) (Mann–Whitney, NS). Trough concentrations were not significantly different in those who were cured (mean 9.3–12.1 mg/L) (Mann–Whitney, NS).

### Discussion

Linezolid concentrations exceeded 4 mg/L (the MIC susceptibility breakpoint for Gram-positive bacteria) for 90% of the dose interval following a dose of 600 mg every 12 h. Therefore the current dose regimen is likely to be effective in the critically ill. Clearance was related to the weight of the patient but not to renal function or haemofiltration. However, in the majority of patients using the standard dosing regimens, teicoplanin trough concentrations were below the 10 mg/L limit recommended by some on the basis of retrospective analysis of efficacy in trials. However, the breakpoint of 4 mg/L was exceeded throughout the dose interval.\textsuperscript{27} The relationship between clearance of teicoplanin and creatinine clearance did not achieve statistical significance because of the variation in serum levels, probably explained by physiological derangements and interventions related to critical illness.

The pharmacokinetics of linezolid have been evaluated in healthy volunteers given single and multiple doses.\textsuperscript{28,29} The elimination half-life of linezolid is usually reported in healthy volunteers as 5–7 h, slightly longer than in this investigation.\textsuperscript{6} Sisson \textit{et al.}\textsuperscript{29} studied the pharmacokinetics of linezolid in 12 healthy volunteers [seven males, five females; mean (s.d.) age, 35 (8.7) years; mean (s.d.) body weight, 73.3 (6.5) kg] who received a single intravenous dose of linezolid 375 mg. They found the mean C\textsubscript{max}, volume of distribution, and elimination half-life of linezolid to be 10.3 ± 1.9 mg/L, 42.3 ± 6.7 L, 7.3 ± 2.0 L/h and 4.4 h, respectively. Linezolid concentrations were >4 mg/L for 5 h, as in the current study. In patients, a population study (n = 318, four samples/patient) reported a volume of distribution at steady state of 65.8 L/65 kg (central 39.6 L/65 kg, peripheral 26.3 L/65 kg), and clearance of 9.09 L/h/65 kg.\textsuperscript{7}

Slatter \textit{et al.}\textsuperscript{10} found a half-life of 3.54 ± 1.37 h in healthy individuals following a single oral dose with a volume of distribution (V) of 29.86 ± 9.42 L. In the present study, the initial volume of distribution was 41.2 L/65 kg and the clearance 3.17 L/h/65 kg. The larger volume of distribution and lower clearance was a result of extended sampling in which the accumulation was more clearly defined. The clearance and volume of distribution obtained from the analysis of the single dose data, which tend to be more in agreement with some literature values, are an overestimate and underestimate, respectively, of those obtained from the full data set. The discrepancy between fits to single dose data and multiple dose data is a consequence of the inadequate characterization of the parameters of the two-compartment model in the single-dose data, particularly when the second half-life is longer than the duration of sampling in the single-dose experiment. Of the covariates we examined, only weight contributed significantly to the inter-individual variations found in linezolid concentration.

Pharmacokinetic parameters of linezolid in adults were not altered by hepatic or renal function, age or sex to an extent requiring dose adjustment, as observed previously.\textsuperscript{30} In a study of 24 subjects with impaired renal function with/without haemodialysis, a single oral dose of linezolid was cleared at the same rate regardless of renal function (92–110 mL/min for patients without dialysis or 77–130 mL/min for those having dialysis).\textsuperscript{7} In 20 patients receiving haemofiltration, the elimination half-life was 4.3 h and clearance 31.2 mL/min.\textsuperscript{31}

The MIC of linezolid effective against 90% of strains of \textit{S. aureus} is 4 mg/L compared with 2 mg/L for \textit{Staphylococcus epidermidis}.\textsuperscript{32} Therapeutic success with linezolid has been related to serum levels exceeding the MIC for 85% of the dose interval or AUC/MIC > 100.\textsuperscript{33} Based on an AUC/MIC target of 100, these data predict a clinical success rate of 80.4%. The clinical and microbiological success rates observed in our associated trial were 78.9% and 70%, respectively.\textsuperscript{21}

Teicoplanin is eliminated predominantly by the kidneys with a total clearance of 11 mL/h/kg in volunteers, burns and cardiac surgery patients.\textsuperscript{13} Renal clearance is between 8.1 and 10 mg/h/kg, one-third of the administered dose being excreted in 24 h. Steady state is reached only slowly, being 93% after 14 days of repeated administration. Elimination is tri-exponential, with half-lives of 0.4–1.0, 9.7–15.4 and 83–168 h. Volumes of distribution are 0.07–0.11 (initial phase), 1.3–1.5 (distribution phase) and 0.9–1.6 (steady state) L/kg.

Using all data points, the clearance estimated was similar to that found in other patient populations (0.69 L/h, 11 mL/h/kg). Clearance estimated from the first dose was much higher, but
the distributional clearance was also high. The volume of distribution using all data points was also in the range observed in other patients.\textsuperscript{13}

\textit{In vitro} the MIC of teicoplanin for 90\% of strains of \textit{S. aureus} is 1 mg/L compared with 4 mg/L for \textit{S. epidermidis}.\textsuperscript{11} The breakpoint for susceptibility is 4 mg/L (S < 4 mg/L, R > 4 mg/L). Retrospective regression analysis of results from 80 patients treated with teicoplanin for \textit{S. aureus} septicemia has suggested the mean pre-dose serum concentration and mean daily dose are significantly greater in those cured compared with those who failed (P < 0.05).\textsuperscript{12} In the elderly, cure rates seemed to exceed 90\% only when the trough was > 10 mg/L. However, this has not been examined by a prospective study of adequate size.\textsuperscript{37}

At a dose of 6 mg/kg/day, trough levels of teicoplanin remain between 7–10 mg/L even with a loading regimen.\textsuperscript{38.39} In leukemic patients, only five of 11 had trough levels >10 mg/L after 120 h in a standard regimen with loading.\textsuperscript{38} Higher trough levels would require additional loading doses and a twice-daily regimen. The lack of toxicity of teicoplanin and the cost of therapy would require additional loading doses and a twice-daily regimen.\textsuperscript{21}

Based on the observed pharmacokinetics, likely pathogen MIC distributions and known pharmacodynamic index target, Monte Carlo analysis predicts linezolid dosage at 600 mg every 12 h to have an adequate therapeutic effect in the critically ill without need for adjustment for renal function. For teicoplanin, a prospective study is needed to confirm if a trough of 10 mg/L is indeed associated with a higher rate of cure than 5 mg/L. If so, serum drug assays or a higher standard dose would be needed to ensure the optimal therapeutic level in some critically ill patients.

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References


