Development of teicoplanin dosage guidelines for patients treated within an outpatient parenteral antibiotic therapy (OPAT) programme

Elspeth Lamont1,2, R. Andrew Seaton2, Merran Macpherson3†, Lindsay Semple2, Emma Bell2 and Alison H. Thomson3–5 *

1Pharmacy Department, Gartnavel General Hospital, NHS Greater Glasgow and Clyde, Glasgow G12 0YN, Scotland, UK; 2Brownlee Centre, Gartnavel General Hospital, NHS Greater Glasgow and Clyde, Glasgow G12 0YN, Scotland, UK; 3Division of Medical Sciences, Western Infirmary University of Glasgow, Glasgow G11 6NT, Scotland, UK; 4Pharmacy Department, Western Infirmary, NHS Greater Glasgow and Clyde, Glasgow G11 6NT, Scotland, UK; 5Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Western Infirmary, Glasgow G4 0NR, Scotland, UK

Received 4 September 2008; returned 2 December 2008; revised 30 March 2009; accepted 2 April 2009

Objectives: The long elimination half-life of teicoplanin facilitates outpatient parenteral antibiotic therapy (OPAT) with thrice-weekly dosing. This study aimed to develop teicoplanin dosage guidelines for OPAT use from routine clinical data.

Methods: Patients received 15–25 mg/kg/day for 3 days, then 15–25 mg/kg thrice weekly. Trough concentrations were measured weekly and doses adjusted to maintain 20–30 or 10–20 mg/L according to clinical condition. Concentration–time data were analysed using the pharmacokinetic package NONMEM and the final model was used to develop new dosage guidelines.

Results: Data from 94 and 36 patients were used for model development and validation, respectively. Patient ages ranged from 15 to 94 years, weights from 43 to 146 kg and estimated CLCR from 9 to 195 mL/min. Teicoplanin concentrations (n = 670) ranged from 6.7 to 66.9 mg/L and a one-compartment model adequately described the data. The typical estimate of CL was 0.542 L/h and changed by 10.6% for every 10 mL/min difference from a CLCR of 66 mL/min. V was 1.62 L/kg. Dosage guidelines based on body weight and CLCR can be expected to lead to a significant improvement in the proportion of concentrations in the range 20–30 mg/L. Alternative doses aimed at lower target concentrations have also been developed.

Conclusions: New dosage guidelines have been developed to support thrice-weekly administration of teicoplanin in an OPAT setting.

Keywords: population pharmacokinetics, therapeutic drug monitoring, extended interval dosing

Introduction

Outpatient parenteral antibiotic therapy (OPAT) is used to facilitate the discharge from hospital of patients requiring medium- or long-term parenteral antibiotic therapy and to avoid admission in those requiring shorter-term therapy. It is associated with an improved quality of life for patients, a reduced risk of healthcare-associated infection and lower treatment costs.1,2 Skin and skin structure infections and bone and joint infections are most suitable for OPAT3 although it has also been used for other infections, including those caused by methicillin-resistant staphylococcal (MRS) species.4,5 Teicoplanin is a useful antibiotic for OPAT because its long elimination half-life supports twice- or thrice-weekly dosing and it is active against MRS species. A key indicator of success involves maintaining serum concentrations above the MIC for the infecting organism.6,7 Positive outcomes have been associated with trough concentrations >20 mg/L in Staphylococcus...
The Glasgow OPAT service has used high, twice- or thrice-weekly dosing regimens of teicoplanin since 2000, usually in combination with a second active oral agent. The duration of therapy for bone and joint infection was agreed between the clinician responsible for the patient and the OPAT service, and was initially up to 12 weeks due to concerns about the risk of relapse in MRS infection. Current practice is a shorter duration of therapy (6–8 weeks). Oral linezolid was not considered due to the potential toxicity associated with prolonged therapy and concerns over early reports of resistance following the antibiotic’s registration. Initial doses of teicoplanin were determined empirically and then adjusted to achieve target concentrations. This approach was used because although standard dosage guidelines are 6 mg/kg, reduced in renal impairment to half or one-third or administered at longer intervals, there were no guidelines for adjusting high-dose intermittent teicoplanin therapy. This led to the need for multiple dosage adjustments and a waste of resources when unnecessarily high doses were prescribed. This study analysed routinely generated teicoplanin concentration data from the OPAT clinic with a population pharmacokinetic approach. Results were used to develop dosing guidelines for thrice-weekly administration. Satisfactory achievement of target concentrations was then evaluated by simulation.

Methods

Patients and protocol

Patients who received teicoplanin through the Glasgow OPAT clinic, and had at least one trough concentration measurement recorded, were eligible for inclusion in the study. Susceptibility testing was carried out using CLSI (formerly NCCLS) guidelines. The isolated implicated Gram-positive organisms from patients were inoculated onto Muller–Hinton (without blood) agar (Oxoid) and incubated overnight in O2 at 37 C with a TEIC-30 disc (Oxoid). No organisms were determined to be ‘resistant’ or ‘intermediate’ on disc susceptibility testing and therefore Teicoplanin Etest strip (MAST) MIC testing was not performed. Data used to construct the population model were collected retrospectively and prospectively from clinic records from November 2000 to January 2003; validation data were collected prospectively between February 2003 and January 2006. Data were collected in the course of routine clinical care and were anonymized before analysis. The study was approved by the West Research and Ethics Committee of the North Glasgow Division, Greater Glasgow Health Board.

Teicoplanin was typically administered by intravenous bolus injection, usually by ‘butterfly’. Other administration devices were occasionally used if necessary. Loading doses of 15–25 mg/kg/day were given for 3 consecutive days followed by 15–25 mg/kg on Mondays, Wednesdays and Fridays. Trough concentrations were measured in all patients who received long-term teicoplanin treatment. Samples were taken once weekly after the longest dosing interval (usually Mondays) and the maintenance dose was then adjusted empirically by the clinician (R. A. S.) with the aim of maintaining target concentrations of 20–30 mg/L for deep-seated infections, such as osteomyelitis, and 10–20 mg/L for bacteraemia or cellulitis. Full blood counts and routine biochemistry were checked at these weekly visits to screen for haematological and renal effects. If any changes in renal function were detected, creatinine concentration was monitored more frequently until renal function stabilized and the dose of teicoplanin was altered as necessary according to the measured concentrations.

The following data were collected from the clinic recording charts: times of drug administration; teicoplanin concentration measurements; age; weight; height; diagnosis; and concurrent antibiotic therapy. Details of creatinine concentration measurements were obtained from patients’ OPAT clinic notes and/or laboratory computer files. The creatinine concentration that was measured closest to the time of each teicoplanin sample was used to estimate CLCR with the Cockcroft–Gault equation using both total body weight (TBW) and ideal body weight (IBW) and the Salazar–Corcoran equation using TBW.

Clinical outcome was determined at the time of discharge from the clinic and recorded in the database according to the following categories: cured (no further treatment required); improved (improvement in clinical parameters with no escalation of therapy required but maintenance or de-escalation oral therapy permitted); no change (no significant clinical improvement and further treatment required, e.g. change in antibiotic or surgical debridement for persistent infective focus); or failed (significant clinical deterioration requiring escalation of antibiotic therapy or surgical debridement).

Drug analysis

Teicoplanin concentrations were determined by fluorescence polarization immunoassay (Abbott Diagnostics Division, Maidenhead, UK) using INNOFLUR® kits (Serodyne Inc., Indianapolis, IN, USA). The assay range was 1.7–100 mg/L and the inter-assay coefficients of variation were 13.6% at 9 mg/L, 3.5% at 35 mg/L and 4.5% at 79 mg/L.

Population pharmacokinetic analysis

Teicoplanin concentration–time data were analysed using NONMEM Version VI with the first-order conditional estimation algorithm with interaction. One- and two-compartment models were compared, a log-additive model was assumed for between-subject variability (BSV) and additive, proportional and combined residual error models were tested. Preliminary investigation of the influence of clinical factors on the pharmacokinetic parameters was conducted using scatter plots and generalized additive modelling, and then potentially descriptive clinical factors were added to the population model. The impact of changes in renal function during therapy was investigated using the ‘difference from baseline’ model described by Wühlby et al. A statistically significant improvement in the model fit was defined as a decrease in the objective function value (OFV) of at least 3.84 (x² test, P<0.05) for the addition of one parameter. Changes in BSV and plots were also used to compare models. External validation was undertaken by using the final population model to predict concentrations and CL in the second cohort of patients and comparing them with measured concentrations and individual CL estimates.

A final population model was then developed using all the data (both the model building and validation datasets). Individual estimates of CL and V generated within this analysis were used to evaluate the new dosage guidelines.
Dosage regimen design

Dosage guidelines were developed from simulations of teicoplanin concentrations using the final population model. Trough concentration–time profiles were constructed using NONMEM with a dataset containing 115 simulated patients with seven values of weight (40, 60, 70, 80, 100 and 120 kg) and up to 15 estimates of CL\textsubscript{CR} for each weight (15, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 110, 125 and 140 mL/min). These values were used to cover the range of weights and renal function expected within this patient group. ‘Standard’ regimens of 15 mg/kg 24 hourly for three doses, then 15 mg/kg thrice weekly (i.e. with intervals of 48, 48 and 72 h) to replicate dosing on Mondays, Wednesdays and Fridays were applied initially and then progressively adjusted until the weekly 72 h trough concentrations for up to 8 weeks of therapy were consistently within the range 20–30 mg/L for all simulated patients. This timescale was used to assess accumulation to steady state in patients with long elimination half-lives. In all cases, doses were calculated from multiples of 400 and 200 mg (the standard strengths of teicoplanin injection). The final dosage guidelines were based on the most robust regimen that consistently achieved concentrations within the target ranges for different combinations of weight and renal function. This approach was repeated for a target trough range of 10–20 mg/L.

The new guidelines were evaluated by predicting the trough concentrations that would have been achieved if the new guidelines had been applied to the patients included in the study. A NONMEM data file was created that contained the new loading and maintenance doses (based on the 20–30 mg/L target) and individual CL and V estimates from the final population analysis. Predictions of trough concentrations at 4, 7, 14, 21 and 28 days were generated, assuming loading over days 1–3 followed by maintenance doses on days 5, 7, 9, 11, 14, 16, 18, 21, 23 and 25. The proportions of predicted troughs within the ranges 20–30, >30 and <10 mg/L, were then calculated and compared with the proportion of measured concentrations within these ranges during the first 4 weeks of therapy. Statistical comparisons were based on the 95% confidence interval (CI) for the difference in proportions.

Results

Patients

During the initial period of data collection, 192 patients attended the OPAT service and received teicoplanin. Concentration measurements (n=472) and detailed dosage histories were available for 94 of these patients and were used to construct the model building dataset. Most of the remaining 98 patients had short courses of teicoplanin and no concentrations were measured before antibiotic treatment was changed or discontinued, however, 20 patients were removed due to missing clinical (n=9), dosage (n=7) or concentration (n=4) data and 4 due to data recording errors. No teicoplanin resistance was identified. There were 52 males and 42 females in the final dataset, with median age 59 years, weight 73 kg and estimated CL\textsubscript{CR} 66 mL/min. Duration of treatment in the dataset had a median of 34 days and ranged from 3 to 102 days. The validation dataset comprised 198 concentration measurements from 36 additional patients (26 males) who had similar clinical characteristics to those in the model building dataset, although they were heavier (median weight 95 kg compared with 73 kg). Forty-nine per cent of patients in the model building dataset and 58% in the validation dataset were >20% above their IBW.

Clinical outcome

Clinical outcomes are summarized in Table 2. Eighty-nine patients were treated for deep-seated infections, of whom 38%...
were cured, 53% improved, 2% were unchanged and 7% failed treatment. The remaining 41 patients had non-deep-seated infections, such as cellulitis and wound infections. Of these patients, 85% were cured, 10% improved, 2.5% failed and one was lost to follow-up. Sixty-nine per cent of patients received at least one other antibiotic, the most common being sodium fusidate (25%), rifampicin (20%), a penicillin or cephalosporin (14%) and ciprofloxacin (9%). Fifteen per cent of patients received two or more additional antibiotics.

Trough teicoplanin concentrations were maintained >20 mg/L for the duration of therapy in 48% of the patients with deep-seated infections who were cured or improved and in four of the eight patients whose conditions were unchanged or who failed to respond. In most cases, low concentrations were only observed at the start of therapy. After the first measurement, concentrations were maintained >20 mg/L in 59% of patients who were cured or improved. In the non-deep-seated infection group, 92% of patients had concentrations >10 mg/L and 33% had concentrations >20 mg/L for the duration of therapy. One patient, who had cellulitis, developed sepsis and was withdrawn from the OPAT programme.

Teicoplanin therapy was stopped due to neutropenia in two (1.5%) patients, one of whom had a previous history of cytopenia prior to commencing teicoplanin. Mean (SD) concentrations in these two patients were 23.2 (2.2) and 37.1 (6.4) mg/L. A 20% decrease in estimated CL_{CR} during the course of treatment was identified in 10 patients (8%), 6 of whom had at least one teicoplanin concentration measurement >30 mg/L. In five of these patients, teicoplanin therapy was discontinued within 3 weeks without changing the dose. The highest teicoplanin concentration measurement in this group was 31 mg/L. The other five patients had courses that lasted 6–8 weeks and their doses were all reduced. Renal function declined, then improved during treatment in three of these patients. Fifty-eight per cent of patients who had no change in renal function had at least one measurement >30 mg/L. Mean (SD) teicoplanin concentrations were significantly higher in the patients whose renal function declined [32 (9) mg/L] compared with patients who had stable renal function [27 (9) mg/L, 95% CI of difference 2.5–7.5 mg/L].

**Population pharmacokinetic model**

Although two- or three-compartment models are usually used to describe teicoplanin pharmacokinetics, the present data comprised trough concentration measurements and could only support a one-compartment model. Residual error had a proportional structure. A linear model using CL_{CR} estimated from the Cockcroft–Gault equation with TBW best described CL. Inclusion of this factor with an intercept reduced the OFV by 65 points and BSV in CL from 43% to 23%. Other CL_{CR} estimates did not provide such good fits and the parameters of the change from baseline model were poorly estimated with no improvement in BSV. V was better described by IBW than TBW.

External validation with the second cohort of patients identified no bias in the predictions of concentrations or CL and acceptable imprecision (median difference in concentrations 16% and in CL 9%).

The final parameter estimates obtained when the combined model building and validation datasets were analysed were similar to those obtained with the model building data alone and are shown in Table 3. The final model described a typical CL of 0.542 L/h for a patient with a median CL_{CR} of 66 mL/min with a 10.6% change for every 10 mL/min above and below this value, i.e. CL (L/h) = 0.542 × [1 + 0.0106 × (CL_{CR} − 66)]. The typical value of V was 1.62 L/kg and the mean derived elimination half-life was 134 h. Figure 1 shows the observed versus population and individual predicted concentrations from this model.

**Dosage guidelines**

Loading and maintenance dosage guidelines developed from the final population model are presented in Tables 4 and 5. The simulation profiles for the 20–30 mg/L target range predicted the weekly 72 h post-dose troughs to have a mean (SD) of 26.5 (2.6) mg/L and range of 19.6–32.7 mg/L over the 8 week simulation period. With the lower target of 10–20 mg/L, the corresponding mean (SD) was 15.8 (2.2) mg/L with a range of 11.0–21 mg/L. If concentrations of 5–10 mg/L are desired, the lower doses should be halved.
When trough concentrations were predicted for each patient in the study by using the new guidelines and their individual CL and V estimates, there was a significant improvement in the proportion of concentrations within the target range compared with those actually observed during the first 4 weeks of therapy. The percentage of concentrations within the range 20–30 mg/L.
increased by 29% (95% CI 23%–86%) from 45% to 74%, the percentage >30 mg/L fell by 21% (95% CI 26%–62%) from 34% to 13% and the percentage <10 mg/L fell by 0.8% (95% CI –0.4% to 2.1%, not significant) from 1.4% to 0.6%. No concentrations were predicted to lie >60 mg/L. The total amount of drug actually administered in this group was 680200 mg and this would have been reduced to 496200 mg (a reduction of 27% and a potential saving of ~£13900) if the new guidelines had been followed. If the lower dosage guidelines had been applied, 12% of trough concentrations would have been expected to lie <10 mg/L, 78% in the range 10–20 mg/L and 10% >20 mg/L.

Discussion

This study used teicoplanin concentration data collected from a routine OPAT clinic to develop thrice-weekly dosage guidelines to achieve different target concentration ranges for 72 h trough concentrations. A preliminary evaluation suggested that these target concentrations would be achieved more consistently with the new guidelines than by using an empirical approach.

Patients attending the OPAT clinic had a range of infections. Success rates of 91% in deep-seated infections and 95% in other infections suggested that the thrice-weekly schedule was effective. Furthermore, the high-dose thrice-weekly protocol produced rates of both neutropenia (1.5%) and nephrotoxicity (8%) that were consistent with literature reports for standard-dose teicoplanin therapy of 2.2% for haematological changes and 6% for nephrotoxicity. These observations suggest that the target concentration ranges used in this study were reasonable. However, the study was neither powered nor aimed to examine relationships between concentration and clinical outcome or toxicity. Although patients whose renal function declined had higher concentrations than those whose renal function was stable or improved, a reduction in renal function would lead to greater accumulation of teicoplanin, therefore it is not possible to draw conclusions about concentration-related toxicity from these data. However, if renal function alters and teicoplanin therapy is still necessary, it would be reasonable to adjust the teicoplanin dose according to the guidelines. Where possible, monitoring the teicoplanin concentration would be helpful to confirm that the dose adjustment is appropriate.

Although previous studies have identified a bi- or tri-exponential decline in teicoplanin concentrations, samples in the present study were typically withdrawn 72 h after the previous dose and at least 1 week of therapy and, consequently, distribution characteristics could not be characterized. The typical elimination half-life derived from the population model averaged 134 h overall, increasing from 121 h in patients with normal renal function to 193 h in mild and 220 h in moderate renal impairment. These values are similar to estimates of 83–159 h in healthy volunteers but lower than the 289 h previously reported in moderate renal impairment.

The identification of estimated CLCR as the best predictor of teicoplanin CL is consistent with previous findings. Many of the patients were obese and although IBW is often used to estimate CLCR in such patients, data to support this approach are limited. In the present study, TBW provided a better fit of the data, which is consistent with the results of previous studies with vancomycin and daptomycin.

The typical CL of 0.542 L/h (9 mL/min) is similar to the value of 0.57 L/h reported by Soy et al. and individual estimates of teicoplanin CL in patients with varying degrees of renal impairment were consistent with the findings of Lam et al. The population estimate of V obtained in this analysis (1.62 L/kg) is also consistent with previously reported values in healthy volunteers (1.4 L/kg) and in patients with endocarditis. The better relationship between V and IBW rather than TBW might reflect the higher proportion of patients who were overweight. No previous studies have examined the relationships between the V of teicoplanin and TBW or IBW in obesity; indeed, previous population analyses have failed to even identify a clear relationship between V and weight. Furthermore, even with vancomycin, which has been studied more extensively, comparisons of TBW and IBW have been inconclusive with respect to V.

When the population model based on the model building dataset was used to predict concentration and CL estimates in a separate group of patients, the predictions were unbiased but relatively imprecise. This may suggest the need for concentration monitoring, even with individualized dosing, if specific target concentrations are desired. When all the data were analysed together, the final parameter estimates were similar to those obtained with the population model, indicating consistency.

The principal aim of this study was to develop loading and maintenance dosage guidelines for use in the OPAT clinic. This was achieved by predicting trough concentration profiles for an 8 week period for simulated patients with weight and CLCR values that spanned the ranges observed in the patient group. Doses were constrained to multiples of 200 mg, to reduce waste and simplify administration, and the upper CLCR estimate for the guidelines was set to 120 mL/min to avoid potential overdosing in patients with non-physiological estimates of CLCR resulting from the use of actual body weight (grossly obese patients) or a low creatinine concentration in the Cockcroft–Gault equation. Although twice-weekly dosing may have sufficed in patients with moderate renal impairment, a fixed schedule of thrice-weekly dosing was used for simplicity. Dosage guidelines were designed to achieve 72 h post-dose troughs (the lowest value each week) of 20–30 and 10–20 mg/L.

A further evaluation of the dosage guidelines was undertaken by examining the predicted trough concentrations that would have been achieved had the patients received doses according to the new guidelines. If the guidelines had been followed, it was expected that 75% of the measured concentrations would have been in the range 20–30 mg/L, which was significantly better than was observed with the empirical guidelines that were in use at the time of the study (44%). Furthermore, several patients would have received lower doses, resulting in a significant reduction in the proportion of unnecessarily high concentrations and a lower cost. A further examination of these data revealed that if TBW rather than IBW had been used for the loading dose, the percentage within the target range would only fall to 71%. This indicates that, for simplicity, TBW could be used for both loading and maintenance doses.

In conclusion, a population pharmacokinetic analysis of teicoplanin concentrations generated routinely within an OPAT clinic has been used to develop new sets of dosage guidelines for thrice-weekly administration. Dosage regimens are adjusted according to desired target trough concentrations, which depend
Teicoplanin dosing in OPAT

on the clinical condition being treated, and according to renal function. Introduction of these new guidelines should reduce the incidence of excessive concentrations, cut the costs of teicoplanin therapy by reducing the dose and improve the efficiency of the service by reducing the need for dosage alterations.

Acknowledgements

We would like to thank the staff of the Clinical Microbiology Department, Western Infirmary, Glasgow, Scotland, UK, for analysing the teicoplanin concentrations and Dr Anne Marie Kärcher for microbiology advice. Preliminary results from this study have been published in conference abstracts [Lamont et al. PAGE. Abstracts of the Annual Meeting of the Population Approach Group in Europe. PAGE 13 (2004) Abstract 481 (www.page-meeting.org/?abstract=481) and Lamont et al. Ther Drug Monit 2005; 27: 227].

Funding

E. L. was an MSc student funded by NHS Education for Scotland. The OPAT clinic was initially funded by a Scottish Executive Health Department grant as a designed healthcare initiative and then through the UK NHS as a routine clinical service. There was no additional funding for the study itself.

Transparency declarations

None to declare.

References