Population pharmacokinetics of teicoplanin and attainment of pharmacokinetic/pharmacodynamic targets in adult patients with haematological malignancy

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Running title: Teicoplanin PK in haematological malignancy patients

Abstract

Objectives: To describe the population pharmacokinetics of teicoplanin in adult haematological malignancy patients receiving higher than standard doses and to perform Monte Carlo simulations to determine dosing regimens associated with optimal teicoplanin concentrations.

Methods: This was a hospital-based clinical trial (EudraCT 2013-004535-72). Nine blood samples were collected on Day 3, plus single trough samples on Days 7 and 10, and 24 and 48 h post last dose. Teicoplanin minimum inhibitory concentrations were determined for Gram-positive isolates from study patients. Population pharmacokinetic analyses and Monte Carlo dosing simulations were undertaken using Pmetrics®.

Results: Thirty adult haematological malignancy patients were recruited with a mean (SD) loading dose, age, total body weight and creatinine clearance of 9.5 (1.9) mg/kg, 63 (12) years, 69.1 (15.8) kg and 72 (41) mL/min, respectively. A three-compartment linear pharmacokinetic model best described the teicoplanin concentration data. Covariates supported for inclusion in the final model were creatinine clearance for clearance and total body weight for volume of the central compartment. The median (IQR) area under the concentration-time curve from 48-72 h ($AUC_{48\text{-}72h}$) was 679 (319) mg.h/L. There was a strong correlation between the $AUC_{48\text{-}72h}$ and trough concentration at 72 h (Pearson correlation coefficient 0.957, P<0.001). Dosing simulations showed that administering five loading doses 12-h, stratified by total body weight and creatinine clearance, increased the probability of achieving target concentrations within 72 h.

Conclusions: To increase the number of patients achieving optimal teicoplanin concentrations an individualised dosing approach, based on body weight and creatinine clearance, is recommended.

Introduction

After nearly three decades of clinical use, teicoplanin has maintained an important niche in the antibiotic arsenal for the treatment of Gram-positive infections in patients with haematological malignancy owing both to its activity against meticillin-resistant staphylococci and to its good safety profile.[1] However, the increasing prevalence of teicoplanin-resistant organisms is posing new challenges.[2-4] To conserve the integrity of this valuable antibiotic, it is imperative that it is used wisely.

Inadequate antibiotic exposure in patients with haematological malignancy may result in a considerable increase in infection-related morbidity and mortality.[5] Sub-therapeutic concentrations are also regarded as a risk factor for the development of microbiological resistance to glycopeptides.[6] Furthermore, the frequent antibiotic courses prescribed for these patients due to infections that commonly occur in the presence of profound immunosuppression, predisposes these patients to infection from less susceptible microorganisms.[7] Therefore, optimal teicoplanin doses at the commencement of therapy should be considered an important goal to ensure rapid achievement of therapeutic concentrations.[8] However, this goal can be confounded by use of dosing regimens that do not account for the pathophysiological changes encountered in patients with haematological malignancy.[8, 9]

As teicoplanin is a hydrophilic, renally cleared and highly protein bound antibiotic, it is considered to be at high risk of pharmacokinetic (PK) variability in the presence of various pathophysiological conditions, many of which occur commonly in patients with haematological malignancy.[8, 10] Sepsis, fluid overload, effusions, hypoalbuminaemia and altered renal function are common conditions in these patients and, since these situations may often coexist in the same patient, drug dosing requirements can be difficult to predict.[9, 10] This represents a significant challenge to clinicians given that dosing regimens have not been developed for these patients.

The ratio of the area under the concentration-time curve to the minimum inhibitory concentration (AUC/MIC) is thought to be the pharmacokinetic/pharmacodynamic (PK/PD) index associated with teicoplanin efficacy,[11] although the specific PK/PD ratio that should be targeted for teicoplanin therapy is not well defined. Two small clinical studies in patients with meticillin-resistant *Staphylococcus aureus* (MRSA) infection have demonstrated that an AUC of ≥750-800 mg.h/L on Day 3 for MRSA isolates with an MIC of ≤1 mg/L was associated with success.[12, 13] However, the requirement of multiple samples to calculate AUC is not feasible for most units and trough concentrations are considered to be a more practical marker for teicoplanin efficacy.[14] The Summary of Product Characteristics (SmPC) specifies a trough concentration target of ≥10 mg/L for most infections,[15] although studies in patients with haematological malignancy have suggested that higher trough concentration targets may be appropriate.[8, 16] To achieve these targets early in therapy, higher loading doses have been suggested,[8, 16] but there is a lack of data available on the ability of empiric dosing schedules to achieve PK/PD targets thought to be associated with clinical success. Previous PK studies of teicoplanin in haematological malignancy patients were based on relatively sparse sampling schedules which may not fully capture the PK properties of teicoplanin. The objectives of this study were to describe the population PK of teicoplanin in adult patients with haematological malignancy based on rich, high quality data, following administration of a new high dose regimen. We then aimed to use this model to perform Monte Carlo simulations to inform dosing regimen selection in terms of the likelihood of achieving therapeutic targets.

Patients and methods

Setting

This single-centre, prospective study was conducted at Tallaght Hospital, a major teaching hospital in Dublin, Ireland. Ethical approval was obtained from the Tallaght Hospital/St James's Hospital Joint Research Ethics Committee (REC reference 2013/12/01). The study protocol was approved by the

Health Products Regulatory Authority (Clinical Trial Number CT 900/545/1), and the trial was registered with the European Clinical Trials Database Registry (EudraCT number 2013-004535-72). The study was conducted following the guidelines of the Declaration of Helsinki. Written informed consent was obtained from all patients.

Study population

The inclusion criteria were: (i) diagnosed with a haematological malignancy; (ii) age ≥18 years; (iii) treated with teicoplanin for >48 h; (iv) intravascular catheter present; and (v) written informed consent obtained. The exclusion criteria were: (i) receiving renal replacement therapy; (ii) admitted to the Intensive Care Unit; (iii) incapable of comprehending the nature and scope of the trial; and (iv) blood sampling personnel/analyst/processing equipment not available.

Dosing regimen

Teicoplanin (Targocid®, Sanofi, Dublin, Ireland) was administered intravenously by slow bolus injection. The hospital dosage regimen was 600 mg (or 800 mg if weight >80 kg) 12-h for three doses followed by 600 mg (or 800 mg if weight >80 kg) once daily. However, prescribed dosing regimens were at the discretion of treating physicians and the hospital dosage regimen was not always followed.

Blood sampling, handling, storage and measurement

For each patient, nine blood samples were collected on Day 3: pre-dose (24 h post-last-loading dose), and then at 5 min, 30 min, 1, 2, 4, 6, 12 and 24 h post-dose. Single trough samples were taken on Days 7 and 10 (when applicable) and 24 and 48 h post-last-dose (when possible).

Samples were immediately refrigerated and centrifuged within 6 h at 3000 rpm for 10 min. The supernatant was stored at -80°C. The samples were shipped on dry ice by a commercial biopharmaceutical shipping company (Quick International Couriers UK Ltd) to Pathology Queensland, Brisbane, Australia, for bioanalysis. Serum teicoplanin concentrations were determined using validated HPLC method as described by Roberts et al.[14]

Determination of creatinine clearance (CL_{CR})

Urine was collected over a 24 h interval on Day 3. The volume of urine was measured and a 1mL aliquot stored at -80°C. Urine creatinine concentration was determined locally using an enzymatic method performed on a Roche/Hitachi Cobas C702 AutoAnalyzer system (Roche Diagnostics GmbH, Mannheim, Germany). Urine volume, serum creatinine concentration on the day of the urine collection and urine creatinine concentration were used to calculate the measured CL_{CR}.

MIC testing

The identification of isolates from study patients was determined locally by broth microdilution using a VITEK®2 system (bioMérieux UK Ltd., Basingstoke, UK) as per routine care. Teicoplanin MICs of Gram-positive isolates from blood cultures taken from study patients were determined locally with MIC test strips (Liofilchem, Italy).

Additional data collection

Additional clinical and demographic data including age, body weight, height, serum albumin concentration, blood counts, 24 h fluid balance on Day 3 and measures of illness severity including the Multinational Association for Supportive Care in Cancer risk-index score,[17] and the Charlson co-morbidity index,[18] were collected.

Population PK modelling

Two- and three-compartment models were developed with the non-parametric adaptive grid algorithm within the Pmetrics package for R (Los Angeles, CA, USA).[19] Elimination from the central compartment and intercompartmental distribution were modelled as first-order processes using differential equations. The AUC from 48-72 h ($AUC_{48\text{-}72h}$) was also calculated.

Demographic and clinical characteristics that were considered biologically plausible for affecting teicoplanin PK were tested for inclusion as covariates. Individual Bayesian estimates for clearance (CL) and volume of the central compartment (V_c) obtained from the selected structural model were firstly plotted against covariate values to assess relationships. If a relationship between the covariate and the PK parameter was observed, then the covariate was tested for inclusion in the population model. If

inclusion of the covariate resulted in a statistically significant improvement in the log-likelihood value (P<0.05) and/or improved the goodness-of-fit plots, it was supported for inclusion in the final model.[20]

Model diagnostics

The model goodness-of-fit was evaluated by visual inspection of the observed-predicted scatter plots, the coefficient of determination (R^2) of the linear regression of the observed-predicted values, and the slopes and intercepts of the regression.[20, 21] Statistical comparisons were made using the log-likelihood ratio test, where twice the log-likelihood difference (LLD) was evaluated against a chi-square distribution (χ^2) with the appropriate number of degrees of freedom (df).[21] Predictive performance evaluation was based on mean weighted error of predictions minus observations (bias) and bias-adjusted mean weighted squared error of predictions minus observations (imprecision) of the population and individual prediction models.[20, 21]

Probability of target attainment (PTA)

Monte Carlo simulations (n=1000) were performed using the final covariate model in Pmetrics to determine the PTA for various dosing regimens. A dosing regimen was considered acceptable if the PTA was ≥90%. IV teicoplanin loading doses ranging from 6-30 mg/kg, administered either 12-h for three doses with one further dose 24 h later, or 12-h for five doses, to a standard 70 kg patient with a CL_{CR} of 70 mL/min were simulated. Seven levels of renal function (CL_{CR} 20, 40, 70, 90, 120, 140 and 170 mL/min), which reflected the distribution of values observed in the study cohort, were also tested. The PTAs for achieving a target trough concentration at 72 h ($trough_{72h}$) of ≥20 mg/L, and an $AUC_{48\text{-}72h}$/MIC of ≥800, were calculated. These targets were based on those suggested from previously published studies.[8, 13, 16] IV teicoplanin maintenance doses ranging from 2-30 mg/kg once daily to a 70 kg patient with various CL_{CR} values (CL_{CR} 20, 40, 70, 90, 120, 140 and 170 mL/min) were also simulated. The PTA for achieving a target trough concentration on Day 7 of ≥20 mg/L was calculated. The PTA (risk) of achieving a trough concentration on Day 7 of ≥60 mg/L, the suggested upper limit for teicoplanin trough concentrations,[22] was also calculated.

Statistical analyses

All statistical analyses were conducted using IBM SPSS Statistics for Windows v. 22 (IBM Corp., Armonk, NY) or Minitab 16 Statistical Software (Minitab Ltd., Coventry, UK). Data were described as the mean ± SD or the median (IQR) for continuous variables, and as the number (%) for categorical variables, as appropriate. Correlation between continuous variables was evaluated using the Pearson correlation coefficient (*r*). Statistical significance was defined as $P<0.05$.

Results

Thirty patients with suspected or confirmed Gram-positive infection were recruited into the study per protocol. Overall, the cohort was of older age, with mild renal impairment, low serum albumin concentrations and severe neutropaenia. A summary of demographic and clinical characteristics of included patients is provided in Table 1. A CL_{CR} of 1 mL/min was assumed for one patient based on the urine output of ~10 mL on Day 3.

Serum teicoplanin concentrations

In total, 352 serum teicoplanin concentrations were analysed. The median (IQR) trough concentrations at 48 h and 72 h were 15.9 (7.6) mg/L and 18.5 (7.9) mg/L, respectively. The median (IQR) teicoplanin $AUC_{48\text{-}72h}$ was 678.8 (319.3) mg.h/L. There was a significant correlation between the teicoplanin $AUC_{48\text{-}72h}$ and $trough_{72h}$ (r=0.957, P<0.001). The regression model for predicting $AUC_{48\text{-}72h}$ from $trough_{72h}$ was: $AUC_{48\text{-}72h} = 146.0 + 28.1\ trough_{72h}$ (R^2=0.917, P<0.001). According to this model, a $trough_{72h}$ of 20 mg/L is associated with an $AUC_{48\text{-}72h}$ of 707 mg.h/L (95% CI 576-838 mg.h/L).

Teicoplanin MICs

Antibiotic susceptibility testing was conducted on 28 CoNS isolates from blood cultures taken from study patients. Of these, 25 were meticillin-resistant (89.3%). Teicoplanin MICs for CoNS isolates ranged from highly susceptible to fully resistant (0.125-8 mg/L), with a median (IQR) of 1.5 (1.2) mg/L.

Pharmacokinetic model building

The teicoplanin concentration-time data were best described by a three-compartment linear model, which was associated with a significant reduction in the log-likelihood value compared to the two-compartment model (LLD=232, $\chi^2(df2) = 13.82$, $P<0.001$). This model included zero-order input of teicoplanin into the central compartment, first-order inter-compartmental distribution and first-order elimination from the central compartment. The only covariates that improved the fit of the model were, for CL, CL_{CR}, and for V_c, TBW.

The final models for CL and V_c were as follows:

$TVCL = CL \times [1 + CL_{slope} (CL_{CR} – 70)]$

$TVV_c = V_c \times (TBW/70)$

where TVCL is the typical value of clearance for an individual patient, CL is the population parameter estimate of clearance for a patient with a CL_{CR} of 70 mL/min, and CL_{slope} is the proportional change in CL with CL_{CR}. TVV_c is the typical value of volume of the central compartment for an individual patient and V_c is the population parameter estimate of volume of the central compartment for a patient with a TBW of 70 kg.

The population PK parameter estimates from the final covariate model are provided in Table 2. The final model described a median CL of 0.524 L/h for a patient with a CL_{CR} of 70 mL/min with 9.0% change for every 10 mL/min above and below this value, i.e. $CL (L/h) = 0.524 \times [1 + 0.009 (CL_{CR} - 70)]$. The median value of V_c was 0.058 L/kg. The diagnostic plots to confirm the goodness-of-fit of this model are shown in Figure 1.

Dosing simulations

The final covariate model was used for Monte Carlo simulations and PTA for achieving targeted teicoplanin exposures ($trough_{72h}$ of ≥20 mg/L and $AUC_{48\text{-}72h}$/MIC of ≥800). The results for the various teicoplanin loading dose regimens are shown in Figure 2. These simulations showed that higher loading doses and increasing the number of loading doses administered resulted in an increased PTA at 72 h. The effect of CL_{CR} on PTA for $trough_{72h}$ is shown in Supplementary Figure 1. These simulations showed that a higher CL_{CR} was associated with a reduced PTA. A summary of dosing

regimens (loading and maintenance doses) associated with a probability of ≥90% for achieving a target trough concentration of ≥20 mg/L at 72 h and on Day 7, together with the probability (risk) of achieving a trough concentration of ≥60 mg/L on Day 7, is provided in Table 3.

Discussion

The results of this study suggest that standard teicoplanin dosing regimens are not suitable for patients with haematological malignancy. An individualised dosing approach may be particularly appropriate for these patients due to the high PK variability observed between patients. Using Monte Carlo simulations, dosing regimens associated with a high likelihood of attaining target teicoplanin concentrations were determined. These simulations suggested that stratifying doses according to body weight and renal function may minimise the number of patients with suboptimal teicoplanin exposures.

Many studies have questioned whether standard doses of teicoplanin, such as those specified in the SmPC, can reliably produce timely therapeutic trough concentrations in clinical practice and there is now an abundance of evidence, particularly for deep-seated staphylococcal infections, suggesting the need for higher doses .[6, 22-24] The need for higher doses and higher target trough concentrations is now recognised for bone and joint infections and infective endocarditis, with the SmPC recommending 3-5 loading doses of 12 mg/kg 12-h followed by 12 mg/kg once daily.[15] Two prominent PK studies of teicoplanin in haematological malignancy patients, of a similar size to the current study, have been published previously and these studies suggested a need for high loading doses of teicoplanin in these patients.[8, 25] However, these studies fitted comparatively sparse sampling data to a two-compartment PK model. Most early studies of teicoplanin PK in healthy volunteers, based on extensive sampling data, described teicoplanin PK as tri-exponential.[26, 27] Using a two-compartment model for teicoplanin may not fully characterise the very slow distribution of teicoplanin into some tissues and therefore not capture the gradual accumulation of teicoplanin in

the body over time. Furthermore, these previous studies of teicoplanin in haematological malignancy patients did not attempt to stratify dosing according to renal function. This might be particularly important for teicoplanin given that it is known to be virtually completely cleared renally.[23]

There are inconsistencies in the literature as to whether teicoplanin loading doses should be adjusted according to renal function with some authors contending that loading doses should only be adjusted for body weight.[8, 28] Our results demonstrate the potential benefits of adjusting loading doses according to renal function, not necessarily to avoid excessive levels in patients with renal impairment but to avoid sub-therapeutic levels in patients with enhanced renal function. The simulations provided in Supplementary Figure 1 highlight the impact of renal function on achieving target teicoplanin trough concentrations at 72 h. In particular, patients with high CL_{CR} may be problematic unless very high loading doses are employed.

The dosing simulations provided in Figure 2 suggest that administration of an extra loading dose at 36 h increases the likelihood of achieving optimal exposure within 72 h. For a typical haematological malignancy patient, with a TBW of 70 kg and CL_{CR} of 70 mL/min, the simulations suggest a loading regimen of 12 mg/kg 12-h for five doses would be needed to ensure a high likelihood of achieving a target trough concentration of ≥20 mg/L at 72 h. For a 90% PTA of achieving an AUC/MIC target of 800, a loading regimen of 15 mg/kg 12-h for five doses would be adequate for a pathogen with an MIC of 1 mg/L. However, for pathogens with MICs >1 mg/L, which occurred in 57% of CoNS isolates in this cohort, very high loading doses of teicoplanin would be needed to achieve the same level of level of exposure. In these cases, it may be prudent to consider using an alternative antibiotic.

It must also be recognised that repeated exposure to suboptimal concentrations is an important risk factor for the development of teicoplanin resistance.[6] Breakthrough resistance to teicoplanin during treatment for CoNS infection has been documented and resulted in treatment failure.[29] Underdosing should therefore be avoided, but by how much teicoplanin doses need to be increased to suppress emergence of resistance, without compromising safety, has not been determined. The proposed

dosing regimens stratified by CL_{CR} provided in Table 3 were associated with a high likelihood of achieving and maintaining target trough concentrations as well as a relatively low risk of attaining trough concentrations ≥60 mg/L on Day 7; the suggested upper limit for teicoplanin trough concentrations.[22] Further studies are required to establish the teicoplanin exposure necessary to achieve clinical efficacy while simultaneously suppressing emergence of resistance. It has been previously suggested that maintenance doses be administered 12-h to ensure maintenance of trough concentrations close to 20 mg/L.[8] However, a trough concentration of 20 mg/L taken 12 h post-dose is not equivalent to a trough concentration of 20 mg/L taken 24 h post dose in terms of total exposure. Larger total daily doses will, in addition to maintaining target trough concentrations, provide greater total exposure and, as AUC/MIC is considered to be the PK/PD index best associated with glycopeptide efficacy, may be preferable from an efficacy perspective.[11] Indeed, a recently published nonclinical study of vancomycin PD for CoNS infection suggested that AUC/MIC and peak/MIC were the dominant PD indices and that less-fractionated dosing regimens may be associated with increased efficacy and reduced risk of emergence of antimicrobial resistance.[30]

An important finding of this study was the very strong correlation observed between teicoplanin $trough_{72h}$ and $AUC_{48\text{-}72h}$, which supports the use of teicoplanin trough concentrations as a surrogate marker of AUC for therapeutic drug monitoring purposes. Similar findings were reported in a recently published study of teicoplanin in children with haematological malignancy.[5] Furthermore, the results of the current study indicated that a $trough_{72h}$ of 20 mg/L correlated with an $AUC_{48\text{-}72h}$ of ~800 mg.h/L; a target previously associated with efficacy.[13]

The strengths of this study were the high quality, rich sampling data obtained prospectively under clinical trial conditions, following administration of higher than standard teicoplanin doses, to inform our population PK model and dosing simulations. We also used local teicoplanin MIC data from Gram-positive blood isolates taken from study patients to assess PK/PD target attainment. However, we acknowledge that the sample size was small and the data were obtained from a single institution and therefore may not be representative of patients admitted to other institutions. Another notable

limitation is that the PK/PD targets for teicoplanin are not well defined and therefore the dosing recommendations based on the assumed targets of the current study may be different should new targets be established in the future. However, our dosing simulations provide PTAs for dosing regimens covering a range of trough concentration targets. Further studies are needed to clarify the PK/PD target for teicoplanin in neutropaenic patients and to confirm any advantage of higher doses on clinical efficacy together with any increased risk of toxicity. Finally, this study did not address unbound teicoplanin concentrations. As teicoplanin is highly protein bound and as patients with haematological malignancy often have low serum albumin concentrations, altered protein binding might be expected. Further work focussing on unbound teicoplanin PK would be valuable. Nevertheless, as only total teicoplanin concentrations are monitored in practice, the results of this study are clinically relevant.

In conclusion, this study has shown that when haematological malignancy patients are treated with standard teicoplanin dosages many may fail to reach therapeutic targets that may be predictive of clinical success. Increasing both the magnitude and number of loading doses administered increases the likelihood of achieving therapeutic targets early in therapy. Individualised loading and maintenance dosing, according to body weight and renal function, is strongly recommended to ensure attainment of therapeutic teicoplanin concentrations and to reduce the risk of excessive levels developing over time.

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Transparency declarations

Jason Roberts has partaken in consultancies/advisory boards for Infectopharm, Astellas, MSD and bioMerieux; in lectures with MSD and investigator initiated grants with MSD and Cardeas.

All other authors have none to declare.

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Table 1. Demographic and clinical details of the included patients (*n*=30)[a]

Characteristic	
Male sex	14 (46.7)
Age (years)	64 [14]
Haematological malignancy diagnosis	
Acute lymphoblastic leukaemia	1 (3.3)
Acute myeloid leukaemia	7 (23.3)
Chronic lymphocytic leukaemia	1 (3.3)
Hodgkin's lymphoma	1 (3.3)
Non-Hodgkin's lymphoma	13 (43.3)
Multiple myeloma	6 (20.0)
Myelodysplastic syndrome	1 (3.3)
MASCC risk-index score[17]	16 [5]
Total body weight (kg)	69.1 ± 15.8
Creatinine clearance (mL/min)[b]	72 ± 41
Serum albumin concentration (g/L)[b]	29 [4]
Mean loading dose (mg/kg)[c]	9.5 ± 1.9
Mean daily maintenance dose (mg/kg)	10.0 ± 1.8
Duration of therapy (days)	9 ± 4

MASCC, Multinational Association for Supportive Care in Cancer

[a] Data are presented as the mean ± SD or the median [IQR] for continuous variables, and as the number (%) for categorical variables.

[b] Value on Day 3 of teicoplanin therapy.

[c] Administered for three doses at the start of teicoplanin therapy.

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Table 2. Parameter estimates for teicoplanin from the final covariate three compartment population pharmacokinetic model

Parameter	Mean	SD	Coefficient of variation (%)	Median
CL (L/h)	0.490	0.122	24.9	0.524
CL_{slope}	0.010	0.007	71.3	0.009
V_c (L)	4.315	1.132	26.2	4.091
K_{cp} (h^{-1})	1.530	0.234	15.3	1.559
K_{pc} (h^{-1})	0.791	0.148	18.8	0.753
K_{cdp} (h^{-1})	0.525	0.140	26.7	0.478
K_{dpc} (h^{-1})	0.033	0.010	30.1	0.032

CL, typical estimate of clearance for a CL_{CR} of 70 mL/min; CL_{slope}, proportional change in CL with CL_{CR}; V_c, typical estimate of volume of the central compartment for a total body weight of 70 kg; K_{cp}, first-order rate constant for drug distribution from the central to peripheral compartment; K_{pc}, first-order rate constant for drug distribution from the peripheral to central compartment; K_{cdp}, first-order rate constant for drug distribution from the central to deep peripheral compartment; K_{dpc}, first-order rate constant for drug distribution from the deep peripheral to central compartment.

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Table 3. Teicoplanin dosage regimens associated with a probability of ≥90% for achieving trough concentrations of ≥20 mg/L at 72 h and on Day 7, and the probability (risk) of attaining trough concentrations ≥60 mg/L on Day 7, for a patient with a total body weight of 70 kg and various CL_{CR} values

CL_{CR} (mL/min)	Loading dose[a]	Maintenance dose[b]	Probability of attaining trough total concentrations ≥60 mg/L on Day 7
20	10 mg/kg	4 mg/kg	2.2%
40	10 mg/kg	6 mg/kg	1.8%
70	12 mg/kg	6 mg/kg	0.0%
90	15 mg/kg	8 mg/kg	0.0%
120	18 mg/kg	12 mg/kg	0.0%
140	22 mg/kg	15 mg/kg	2.8%
170	25 mg/kg	18 mg/kg	9.9%

CL_{CR}, creatinine clearance

[a] Administered 12-h for five doses

[b] Administered once daily

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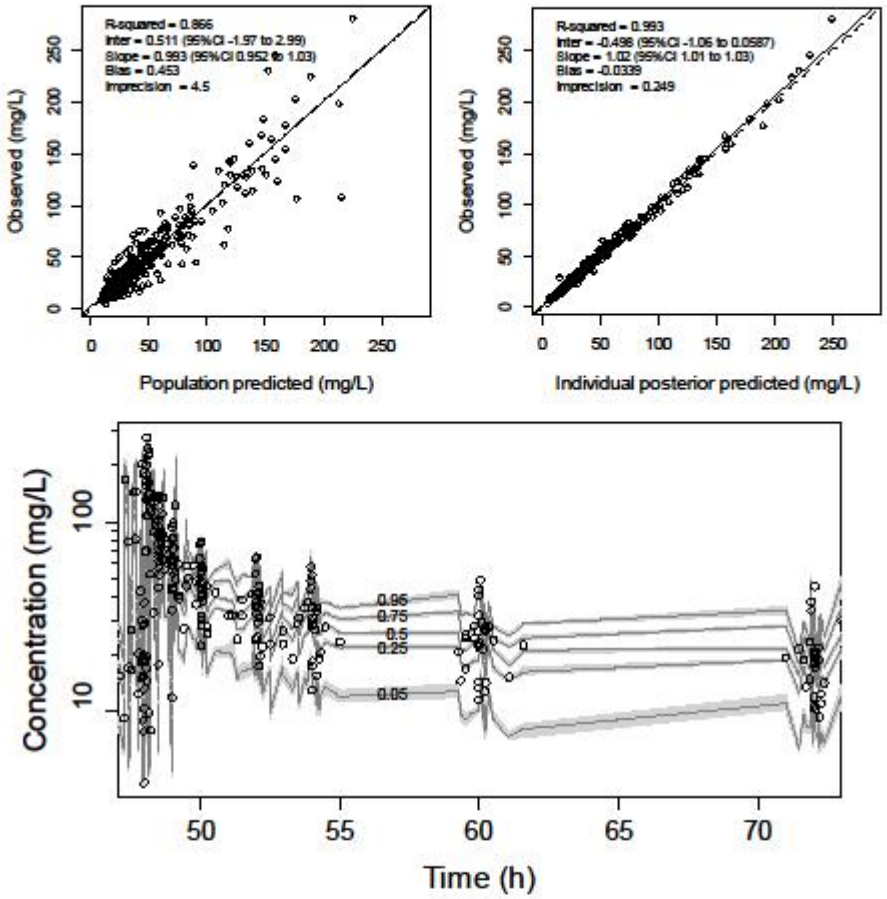
Figure Captions

Figure 1. Diagnostic plots for the final covariate model for teicoplanin. Population predicted versus observed concentrations (top left) and individual posterior predicted versus observed concentrations (top right). Visual predictive check (bottom) showing the percentiles of 1000 simulated teicoplanin concentration-time profiles (lines) superimposed with observed teicoplanin concentrations (circles). The grey shading around the percentiles represents the 95% confidence interval around each percentile. The distribution of the simulated profiles is similar to that of the observed concentrations, suggesting that the model describes the data adequately.

Figure 2. Monte Carlo simulations and probability of target attainment (PTA) for various teicoplanin trough concentrations at 72 h and a target area under the concentration-time curve from 48-72 h to the minimum inhibitory concentration ratio (AUC/MIC) of ≥800, for a standard haematological malignancy patient with a total body weight of 70 kg and a creatinine clearance of 70 mL/min. The teicoplanin loading dose regimens were: four doses administered at 0, 12, 24 and 48 h, or five doses administered at 0, 12, 24, 36, and 48 h. The MIC range is based on the MIC distribution for coagulase-negative staphylococci in the study cohort.

Supplementary Figure 1. Monte Carlo simulations and probability of target attainment (PTA) for trough teicoplanin concentrations at 72 h for a 10 mg/kg teicoplanin dose administered at 0, 12, 24 and 48 h (left plot) and at 0, 12, 24, 36 and 48 h (right plot) to a patient with a total body weight of 70 kg and various levels of creatinine clearance (CLcr).

436 Figure 1



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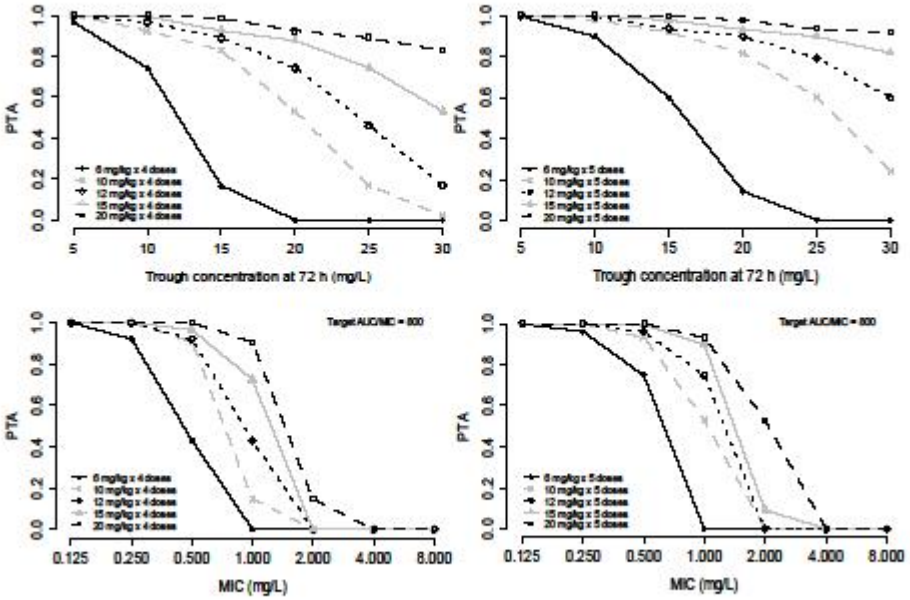
439 Figure 2



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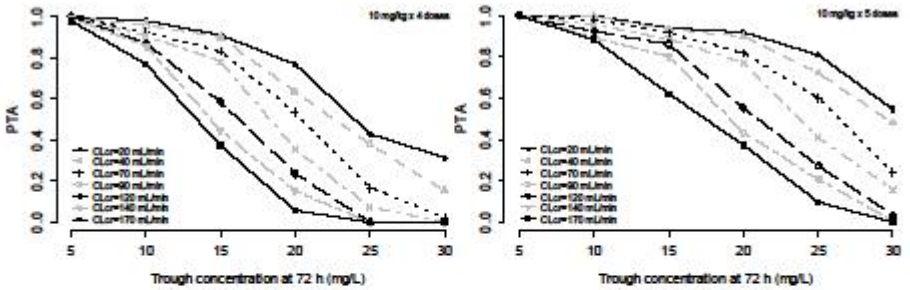
442 Supplementary Figure 1



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