DEVELOPMENT AND EVALUATION OF VANCOMYCIN DOSAGE GUIDELINES DESIGNED TO ACHIEVE NEW TARGET CONCENTRATIONS

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Synopsis

Aims: To develop a population pharmacokinetic model of vancomycin in adult patients; to use this model to develop dosage guidelines targeting vancomycin trough concentrations of 10 – 15 mg/L and to evaluate the performance of these new guidelines.

Methods: All data analyses were performed using NONMEM®. A population pharmacokinetic model was first developed from vancomycin dosage and concentration data collected during routine TDM in 398 patients, then new vancomycin dosage guidelines were devised by using the model to predict vancomycin trough concentrations in a simulated dataset. Individual estimates of CL and V1 were then obtained in an independent group of 100 patients using the population model and the POSTHOC option. These individual estimates were used to predict vancomycin trough concentrations and steady state AUC_{24}/MIC ratios using the current and new dosage guidelines.

Results: The population analysis found that the vancomycin data were best described using a bi-exponential elimination model with a typical CL of 3.0 L/h that changed by 15.4% for every 10 mL/min difference from a CL_{CR} of 66 mL/min. Vss was 1.4 L/kg. The proposed dosage guidelines were predicted to achieve 55% of vancomycin troughs within 10 – 15 mg/L and 71% within 10 – 20 mg/L, which is significantly higher than current guidelines (19% and 22% respectively). The proportion of AUC_{24}/MIC ratios above 400 was also higher; 87% compared to 58%.

Discussion: New vancomycin dosage guidelines have been developed that achieve trough concentrations of 10 – 15 mg/L earlier and more consistently than current guidelines.

244 words

INTRODUCTION

With the rapid increase in the incidence of *methicillin-resistant Staphylococcus aureus* (MRSA) infection and concerns about the clinical consequences of underdosing, achieving target concentrations of vancomycin efficiently has become increasingly important. Traditionally, "peak" and "trough" concentrations were measured and the focus was on preventing toxicity by avoiding what were perceived to be excessive troughs (>10 mg/L).[1] More recently, evidence that trough concentrations of 5 – 10 mg/L might be insufficient to achieve adequate tissue penetration and kill rates for more resistant species has prompted laboratories to recommend a variety of higher target values, up to and exceeding 15 mg/L.[2] These changes reflect current British National Formulary (BNF) recommendations of 10 – 15 mg/L and 15 – 20 mg/L for more resistant strains.[3] Similar targets have also been suggested for pneumonia[4] and meningitis,[5] while continuous infusions of vancomycin which target average steady state concentrations of 15 – 25 mg/L, have been advocated for critically ill patients.[6]

Further support for using higher target concentrations of vancomycin is based on observations that nephrotoxicity is rare with the current formulation,[7] although there is some evidence of an increased risk of nephrotoxicity with co-administration of other nephrotoxic agents, prolonged therapy and concentrations above 10 mg/L.[8,9] More recently, nephrotoxicity has been associated with vancomycin doses above 4 grams per day,[10] trough concentrations above 15 mg/L[11,12] and average steady state concentrations above 28 mg/L.[13]

Despite the current support for using more aggressive vancomycin therapy, a recent review revealed that none of the laboratories surveyed in Scotland had made changes to their hospital dosing recommendations.[2] Furthermore, most established guidelines and nomograms quote only a standard dosage regimen[3] or aim for target concentrations that are generally lower than currently recommended.[14-17] This is reflected within Glasgow, where vancomycin is currently prescribed using dosage guidelines that were developed to achieve trough concentrations of 5 – 10 mg/L,

although current laboratory practice favours BNF recommendations.[3] These observations prompted the need for new dosage guidelines that could achieve these higher targets.

The aims of this study were to develop a population pharmacokinetic model to describe the handling of vancomycin in adult patients from data collected during their routine clinical care, to use the model to develop dosage guidelines aimed at achieving higher trough concentrations and to evaluate the performance of these new guidelines using data collected from an independent group of patients.

METHODS

Study approval

All data collected for this study were obtained during patients' routine clinical care and the population analysis was defined as audit by the West Ethics Committee of the North Division of NHS Greater Glasgow (approval number 99/111, letter dated 16 June 1999). The data collection conducted at Southmead Hospital, Bristol was also designated as audit.

Patients and data collection

Data for population pharmacokinetic model development were collected retrospectively from routine therapeutic drug monitoring (TDM) files of patients who were treated with intravenous (iv) vancomycin therapy between May 1991 and July 2004 at the Western Infirmary, Glasgow and Gartnavel General Hospital, Glasgow and prospectively from patients treated with vancomycin in Southmead Hospital, Bristol (1999 to 2002). Data from 102 of the 398 patients who were included in this population model dataset had been included in a previous population modelling study.[18] A second data set, which was used to evaluate the dosage guidelines, was compiled retrospectively from TDM files of 100 patients who were treated with iv vancomycin between November 2004 and June 2007 at the Western Infirmary, Glasgow. For both data sets, patients aged 16 years or more and who had at least

one vancomycin concentration measurement recorded, were eligible for inclusion. Patients in renal failure who were receiving renal replacement therapy and patients in whom dosage and/or sampling times were missing or not clear were excluded from the analysis.

Information on vancomycin dosage amounts, exact dates and times, infusion length and patient demographic factors was extracted from routine TDM files that had been completed during each patient's treatment. Demographic data collected included patient age, total body weight (TBW), height and gender. Lean body weight (LBW),[19] LBW based on a semi-parametric calculation,[20] ideal body weight (IBW),[21] and body surface area (BSA),[22] were calculated from patient weight, height and gender. Serial measurements of serum creatinine (SeCr) were recorded from TDM files and clinical chemistry electronic records. SeCr measurements below the lower limit of the reference range (60 μmol/L) were set to 60 μmol/L as described previously.[23] Creatinine clearance (CL_{CR}) was calculated using the Cockcroft-Gault equation,[24] the Jelliffe equation,[25] the Salazar Corcoran equation,[26] and the MDRD equation.[27] Additionally, a CL_{CR} estimate was obtained using LBW,[19] and IBW,[21] instead of TBW in the Cockcroft-Gault equation.[24]

Differences in demographic and clinical features between the population model development and evaluation patient groups were examined by calculating the 95% confidence interval (CI) for the difference in proportion or by a Mann Whitney U test or Student's t-test (as appropriate) with significance level set at $p<0.05$.

Vancomycin assay

Vancomycin drug concentrations were analysed by fluorescence polarization immunoassay at the Microbiology Departments of the Western Infirmary (TDx, Abbott Diagnostics, Chicago, USA) or Southmead Hospital (FLx, Abbott Diagnostics, Chicago, USA). The inter-assay coefficients of variation for the TDx were 4.3% at 10.5 mg/L, 2.1% at 31 mg/L and 4.2% at 58 mg/L and for the FLx were 2.5% at 7.0

mg/L, 1.9% at 35 mg/L and 2.0% at 75.0 mg/L. The lower limit of quantification was 2 mg/L for both analysers.

Population pharmacokinetic analysis

Population modelling was performed using NONMEM® (version 6, Globomax Inc.)[28] with a G77 FORTRAN compiler. Analysis and post processing were performed with the aid of the PsN toolkit,[29] and Xpose (Version 4),[30] programmed in the statistics package R.[31]

Single and bi-exponential elimination models were compared and both untransformed and log-transformed vancomycin concentrations were analysed. Inter-individual variability in pharmacokinetic parameters was assumed to be log-linear. Residual error on concentration was described by a combined error model. Covariance between inter-individual variabilities in drug CL and V was examined. All modelling was performed using First Order Conditional Estimation with interaction.

Clinical factors investigated for an influence on the pharmacokinetics of vancomycin were: gender; age; TBW; LBW; IBW; BSA; height; day of therapy; SeCr and all CL_{CR} estimates. Potentially useful covariates were identified by GAM analysis and scatter plots and were then introduced sequentially into the population model. Models were compared visually with a range of plots and statistically using a likelihood ratio test on the differences in the objective function value (OFV) with significance set at $p<0.005$. Changes in inter-individual variability and residual random error were also examined.

Uncertainty in the final population model parameter estimates was assessed using a bootstrap method.[32] In brief, this involves repeated random sampling, with replacement, of the original data set to produce another data set of the same size but with a different combination of subjects. As the number of bootstrap samples approaches infinity, the sample standard deviations of the parameters approach the 'true' (but unknown) standard deviations. In this study, bootstrapping was performed

with the assistance of the PsN toolkit.[29] Mean parameter estimates obtained from 250 bootstrap runs were compared to population mean values.

Development of Dosage Guidelines

A data set was created containing 110 simulated "patients" with a range of weights (40, 50, 60, 70, 80, 90, 100 or 120 kg) and CL_{CR} estimates (15, 20, 25, 30, 40, 50, 60, 70, 80, 90, 100, 110 or 125 mL/min) that spanned the typical patient population. Draft dosage guidelines containing a range of loading and maintenance doses were then tested for their ability to achieve vancomycin trough concentrations of 10 – 15 mg/L during the first 4 days of therapy. Dosage amounts were fixed to multiples of 250 mg and dosage intervals were limited to 12, 24 or 48 hours for practicality. Each individual in the simulated dataset was assigned a vancomycin dosage history then trough concentrations were predicted by running NONMEM® with the population parameter values fixed at the final model estimates. These predicted troughs were compared with the target range of 10 – 15 mg/L. The draft guidelines were then amended for simulated patients whose weight and/or CL_{CR} combinations resulted in vancomycin trough predictions outside the desired range. This process was repeated until final dosing guidelines were created that consistently achieved the target concentrations in the simulated patients.

Evaluation of New Dosage Guidelines

A data file containing all clinical, dosage and concentration data recorded for patients in the evaluation data set was created. Individual estimates of vancomycin pharmacokinetic parameters were then obtained for each patient by MAP Bayesian analysis of their data using the final population model and the POSTHOC option in NONMEM®. These empirical Bayes' estimates were used to predict the trough concentrations that would have been expected during the first 4 days of therapy if each patient had been treated according to the current and the new dosage guidelines. The proportions of concentrations within different ranges during the first 4

days of therapy were compared by determining the 95% confidence intervals of their differences with correction for multiple comparisons. Area under the concentration – time curve for a 24 hour period at steady state (AUC_{24}) was calculated from daily dose amount/CL and average steady state concentration (Css) from dose rate/CL.

RESULTS

Patients and data collection

Data were collected from 398 patients for population model building (including 99 patients from Bristol) and a further 100 patients for evaluation of the new dosage guidelines. Demographic, clinical, dosage and concentration data from both groups are summarised in Table 1. The population model data set comprised 1557 vancomycin concentration measurements and the evaluation data set 171 measurements. The median measured vancomycin concentration was 12.1 mg/L in both data sets. The majority of samples, 64% and 62% respectively, were drawn at least 10 hours after the start of the infusion. There were no significant differences between the population model building and evaluation datasets in terms of patients' initial SeCr values, initial vancomycin dose, vancomycin concentration values or the length of time after the start of infusion that vancomycin concentrations were measured. However, patients in the evaluation group were more likely to be female, to be older, to weigh less and to have lower CL_{CR} estimates (Table 1).

Population modelling

The vancomycin data were best described by a bi-exponential elimination model and results were similar with non-transformed and log-transformed vancomycin concentration data. The final covariate model included CL_{CR} estimated using the Cockcroft-Gault equation based on TBW as the only factor affecting CL; TBW influenced both the volume of the central (V1) and peripheral compartments (V2). Inclusion of CL_{CR} reduced inter-individual variability on CL from 53% to 27%

and the model OFV by 679 points and the addition of TBW reduced inter-individual variability on V1 from 26% to 15% and the model OFV by a further 34 points.

Pharmacokinetic parameter estimates from the final population model are presented in Table 2. The parameter values from the final model obtained from application of bootstrap analysis were similar to the final model developed using the 398 patients, with no parameter difference greater than 10%. A plot of model-predicted versus observed concentrations for the final model based on population parameter estimates and individual parameter estimates is shown in Figures 1a and 1b respectively. Examination of plots of conditional weighted residuals (CWRES) versus time after dose confirmed the appropriateness of the bi-exponential elimination model.

Development and evaluation of dosage guidelines

Table 3 shows the guidelines currently in use within North Glasgow (target trough 5 – 10 mg/L) and Tables 4 and 5 the revised guidelines (target trough 10 – 15 mg/L). Although the doses are generally similar, the new guidelines included a loading dose and tended to recommend higher doses or shorter dosage intervals (i.e. the same daily dose but split and given 12 hourly rather than 24 hourly).

POSTHOC analysis of the evaluation data set encountered problems with non-physiological values when all parameters were estimated therefore only CL and V1 were estimated; V2 and intercompartmental clearance (Q) were fixed at population values. Using these individual CL and V1 estimates, the predicted trough concentrations in the validation data set over the first 4 days of therapy were consistently higher at each time point with the new guidelines (Figure 2a) compared to the old guidelines (Figure 2b). Mean (SD) predicted trough concentrations during this period were also significantly higher with the new guidelines 12.2 (3.4) mg/L, (n = 688) compared to 7.9 (3.3) mg/L with the old guidelines (n = 514). Differences in the number of samples reflect more 12 hourly dosing with the new guidelines. Furthermore, Table 6 shows that the proportions of concentrations within the ranges

10 – 15 mg/L, 15 – 20 mg/L and >20 mg/L were also higher. Overall, within the first 4 days of therapy, 55% of vancomycin trough concentrations were predicted to be within 10 – 15 mg/L with the new dosage guidelines compared with only 19% with the current dosage guidelines. The percentages within the range 10 – 20 mg/L were even higher (71% compared to 22%). Predicted average Css concentration and AUC_{24} in the validation data set were also higher with the new guidelines. Mean (SD) estimates of AUC_{24} were 520 (124) mg.h/L and 436 (104) mg.h/L and mean (SD) Css estimates were 21.7 (5.2) mg/L and 18.2 (4.3) mg/L respectively. Assuming an MIC of 1 mg/L, 87% of patients were predicted to have an AUC_{24}/MIC ratio above 400 and only 4% would be below 350 if the new guidelines were followed, compared to 58% and 24%, respectively, with the current guidelines.

DISCUSSION

This study used data collected during routine TDM to determine population estimates of vancomycin pharmacokinetic parameters, develop new dosage guidelines and evaluate these new guidelines prospectively.

Some of the data that were included in the present population analysis had been analysed previously in an investigation of vancomycin pharmacokinetics in 102 cardiothoracic surgery patients with unstable renal function.[18] This previous study found that data from such patients could be described adequately if serial measurements of creatinine concentration, which indicated renal function changes, were available. Although a mono-exponential elimination model proved adequate in the earlier study, the current analysis found that the data were better described using a two-compartment model. The typical estimate of CL was 3 L/h in both analyses but the influence of CL_{CR} was slightly different; the previous study identified a 20.5% change in vancomycin CL with every 10 mL/min change in CL_{CR} from 66 mL/min compared to only 15.4% in the current analysis. The Cockcroft Gault equation[24] based on TBW provided the best fit of the data overall. Other pharmacokinetic studies have found similar relationships between vancomycin CL and CL_{CR}. Based

on a CL_{CR} of 66 mL/min, CL estimates identified in these earlier studies were typically around 3.0 L/h and ranged from 2.9 to 4.3 L/h.[15, 33-37]

The volume of distribution of vancomycin is generally reported as 0.5 – 0.98 L/kg with an average around 0.7 L/kg[14,15,33,34,37], which is similar to the estimate of V1 (0.7 L/kg) identified in the present study. Although volume of distribution at steady state (Vss) was higher at 1.4 L/kg, both Llopis-Salvia et al[36] and Fernández de Gatta Garcia et al[38] reported even higher estimates (1.7 L/kg TBW) in their population analyses of vancomycin pharmacokinetics. It is possible that differences in the duration of therapy, the pharmacokinetic model used to analyse the data and the clinical characteristics of the patients included in each study may have contributed to these observations.

For both CL and V, a range of weight measurements were tested in the population analysis, and although 19% of patients were clinically obese (Body Mass Index >30 kg/m^2) no clear improvement in the fit of the population model was identified if TBW was replaced by LBW or IBW. These findings are consistent with other studies. Although conflicting results have been reported on the influence of obesity on vancomycin CL and V, TBW is usually recommended for dosage adjustment[39-42] and has practical advantages when applied in a routine clinical environment. However, particular care is required when prescribing for patients who are obese or underweight and close monitoring of vancomycin concentrations is advised to ensure that dosage regimens are appropriate.

The current BNF dosage recommendation for iv pulsed infusion vancomycin has recently been changed to 1000 – 1500 mg twice daily reduced to 500 mg twice daily or 1000 mg daily in patients over 65 years of age[3]. Although these doses are higher than previously recommended, it is not clear what trough concentrations will be obtained with these dosage regimens and there is no guidance on how to adjust for renal impairment. Other published dosage guidelines aim for troughs of 5 – 10 mg/L,[15,17] 5 – 20 mg/L[16] or an average steady state concentration of 15 mg/L.[14] However, to achieve trough concentrations above 10 mg/L, daily doses greater than

2000 mg are usually required for patients with normal renal function, particularly if they are critically ill.[38,42,43] The present study demonstrated that the new guidelines should achieve vancomycin trough concentrations of 10 – 15 mg/L earlier and more consistently than current dosage guidelines. Other indicators of vancomycin efficacy have also been investigated. Moise-Broder et al[44] reported that clinical outcome was significantly better if the AUC_{24}/MIC ratio was greater than 400 in patients with *S. aureus* lower respiratory tract infections and this target ratio has recently been recommended in an American consensus review.[42] In the present study, 87% of patients were predicted to achieve satisfactory AUC_{24}/MIC ratio ratios if the new guidelines were followed. Low AUC_{24}/MIC ratios typically occurred when the individual estimate of CL was higher than predicted from CL_{CR}. Much higher doses or an alternative antibiotic would be required if the MIC was 2 mg/L since only 2% of patients would be likely to achieve an AUC_{24}/MIC ratio above 400. These difficulties prompted the authors of the American consensus review to question the value of vancomycin in the treatment of MRSA infections if the strain has an MIC above 1 mg/L.[42]

The present study has confirmed the importance of giving a loading dose when starting vancomycin therapy, especially in patients with renal impairment, in whom accumulation to steady state will take longer. Although the need for a loading dose has been recognised for many years,[15,45] and has recently been highlighted again,[42] loading doses are absent from the BNF guidelines[3] and are not often used in routine clinical practice.

Figure 2a demonstrates that the new dosage guidelines lead to a greater risk of vancomycin trough concentrations accumulating above 15 mg/L, especially after day 3 of therapy. This emphasises the need for monitoring vancomycin concentrations within the first 3 days to avoid excessive accumulation and potential for toxicity.[9] However, troughs of 15 – 20 mg/L may also simply reflect the flatter profile that the new guidelines aim to achieve. An extension of this principle would be to administer vancomycin by continuous infusion; an alternative approach that is

increasingly being used in routine clinical practice since it is easier to monitor and adjust doses. The pulsed infusion doses recommended in the new guidelines presented here should achieve average steady state concentrations of around 22 mg/L and are therefore compatible with the continuous infusion target concentrations of 15 – 25 mg/L that are commonly advocated[6] and well below the 28 mg/L cut-off identified by Ingram et al[13] as being associated with an increased risk of toxicity. Consequently, a trough of 15 – 20 mg/L does not necessarily indicate a problem; it may simply reflect a flatter profile in a patient with poor renal function. Dosage intervals of 8 hours offer an alternative administration method in cases where the required daily dose is particularly high or could easily be divided into 3, for example, 1000 mg 8 hourly rather than 1500 mg twice daily or 500 mg 8 hourly rather than 750 mg twice daily. Six hourly administration of half the 12 hourly dose would also be feasible but may be difficult to manage on a busy ward. Both options would achieve higher trough concentrations and lower peaks but the same overall exposure (AUC_{24}).

In conclusion, this study has developed new, iv pulsed infusion dosage guidelines for vancomycin following a population analysis of routine vancomycin concentration data. The new guidelines are based on practical doses that are easy to prepare and administer, and reflect current vancomycin target concentrations. A preliminary evaluation of the guidelines using data collected from a separate group of patients indicated that 55% of trough concentrations should be within 10 – 15 mg/L and 71% within 10 – 20 mg/L over the first 4 days of therapy and that satisfactory AUC_{24}/MIC ratios should be achieved in 87% of patients, assuming an MIC of 1 mg/L. However, wide variability in the handling of vancomycin between and within patients indicates that monitoring of concentrations is required to ensure that dosage regimens are appropriate for individual patients.

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TRANSPARENCY DECLARATIONS

None to declare.

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46. FIGURE LEGENDS

Figure 1

Plots of model-predicted versus observed concentrations for the final model based on a) population parameter estimates and b) individual parameter estimates.

Figure 2

Box and whisker plots of the distributions of vancomycin trough concentrations over the first 4 days of therapy predicted from a) the new dosage guidelines and b) the current dosage guidelines using CL and V1 estimates derived from routine data collected from 100 patients.

Table 1: Patient demographic and pharmacokinetic features of the model development and evaluation datasets. Results are presented as number, or median (range).

	Population model building dataset	Dosage guideline evaluation dataset	Statistical comparison
Demographic data			
Number of patients	398	100	
Males (%)	63	50	p = 0.019
Age (years)	66 (16 – 97)	71 (22 – 91)	p < 0.001
Weight (kg)	72 (40 – 159)	65 (35 – 130)	p < 0.001
Initial SeCr (μmol/L)	98 (30 – 573)	94 (55 – 353)	NS
Initial CL_{CR} (mL/min)	64 (12 – 216)	50 (12 – 148)	p = 0.003
Pharmacokinetic data			
Number of samples	1557	171	
Initial dose (mg)	1000 (500 – 1750)	1000 (500 – 1500)	NS
Concentration (mg/L)	12.1 (2.0 – 49.2)	12.1 (2.0 – 29.2)	NS
Samples per patient	3 (1 – 19)	2 (1 – 5)	p < 0.001
Time after start of infusion (hrs)	11.9 (1.1 – 92.3)	12.4 (0.3 – 57.3)	NS
Follow-up period (days)	4.9 (0.5 – 44.4)	2.5 (0.2 – 9.3)	p < 0.001

Table 2: Population parameter estimates based on the final population model.

Population model	Final estimates	RSE %	Bootstrap estimates	95% CI
CL (L/h)	2.99	1.9	2.98	(2.85 - 3.13)
θ_{CRCL}	0.0154	4.3	0.0154	(0.0144 - 0.0165)
V1 (L/kg)	0.675	1.8	0.676	(0.637 - 0.713)
V2 (L/kg)	0.732	0.7	0.775	(0.543 - 1.090)
Q (h^{-1})	2.28	23.7	2.25	(1.68 - 2.90)
η_{CL} (%)	27	14	27	(24 - 31)
η_{V1} (%)	15	40	15	(8 - 21)
η_{V2} (%)	130	20	125	(88 - 150)
η_{Q} (%)	49	29	54	(34 - 81)
Additive error (mg/L)	1.6	7.7	1.6	(1.3 - 1.8)
Proportional error (%)	15	7	15	(12 - 17)

Key: CL = typical estimate of clearance for a CL_{CR} of 66 mL/min, θ_{CRCL} = proportional change in CL with CL_{CR} (calculated using TBW and Cockcroft-Gault equation[24]), Q intercompartmental CL, η = inter individual variability expressed as a percentage, RSE = relative standard error expressed as a percentage coefficient of variation, [#](mL/min)

Table 3: Current vancomycin dosage guidelines.

CL_{CR} (mL/min)	Weight <60 kg	Weight >60 kg
< 20	1000 mg then sample after 24 hrs	1000 mg then sample after 24 hrs
20 - 29	1000 mg 48 hourly	1000 mg 48 hourly
30 - 49	750 mg 24 hourly	750 mg 24 hourly
50 - 59	1000 mg 24 hourly	1000 mg 24 hourly
60 - 69	500 mg 12 hourly	1000 mg 24 hourly
70 - 79	750 mg 12 hourly	750 mg 12 hourly
80 - 100	750 mg 12 hourly	1000 mg 12 hourly
> 100	1250 mg 12 hourly	1250 mg 12 hourly

Key: CL_{CR} estimate based on the Cockcroft-Gault equation[24]

Table 4: New vancomycin loading dose guidelines based on the final population model.

Loading Dose

Weight	**< 60 kg**	**60 – 90 kg**	**>90 kg**
Loading dose	1000 mg	1500 mg	2000 mg

Table 5: New vancomycin maintenance dose guidelines based on the final population model.

Maintenance Dose

CL_{CR} (mL/min)	**Dose (mg)**	**Interval (hrs)**
< 20	500 mg	48 hours
20 - 29	500 mg	24 hours
30 - 39	750 mg	24 hours
40 - 54	500 mg	12 hours
55 - 74	750 mg	12 hours
75 - 89	1000 mg	12 hours
90 - 110	1250 mg	12 hours
>110	1500 mg	12 hours

Key: CL_{CR} estimate based on the Cockcroft-Gault equation[24]. N.B. Higher troughs and lower peaks would be achieved by splitting the total daily dose into 3 or 4 equal portions, for example, 1000 mg 8 hourly instead of 1500 mg 12 hourly or 500 mg 6 hourly instead of 1000 mg 12 hourly.

Table 6: Proportions (%) of predicted vancomycin trough concentrations within different ranges during the first 4 days of therapy.

Predicted concentration range	Current guidelines (n = 514)	New guidelines (n = 688)	Difference in proportion	99% CI of the difference
< 10 mg/L	0.77 (77%)	0.26 (26%)	-0.51	-0.44 to -0.57
10 – 15 mg/L	0.19 (19%)	0.55 (55%)	0.36	0.30 to 0.43
15 – 20 mg/L	0.03 (3%)	0.16 (16%)	0.13	0.09 to 0.17
> 20 mg/L	0.00 (0%)	0.03 (3%)	0.03	0.01 to 0.04

Key: n = the number of predicted trough concentrations during the first 4 days in the 100 evaluation patients.

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Figure 1 a

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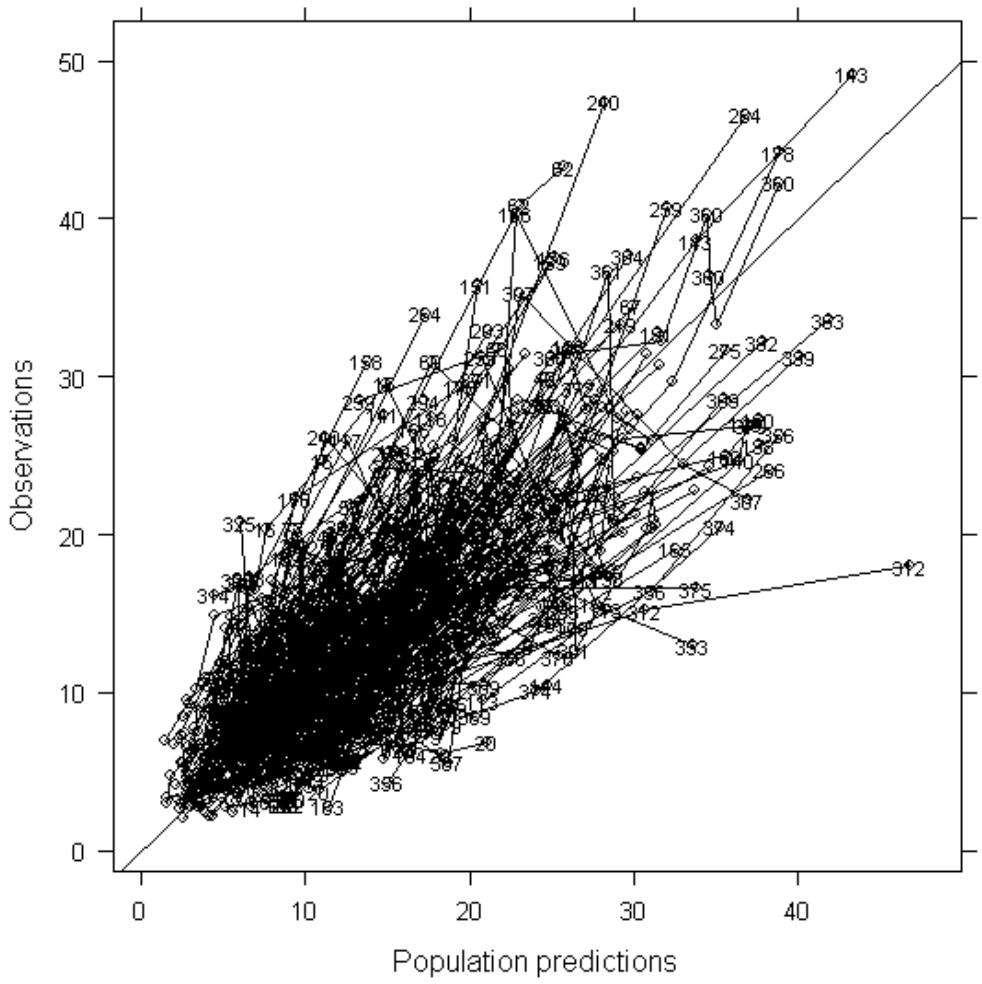

Figure 1 b

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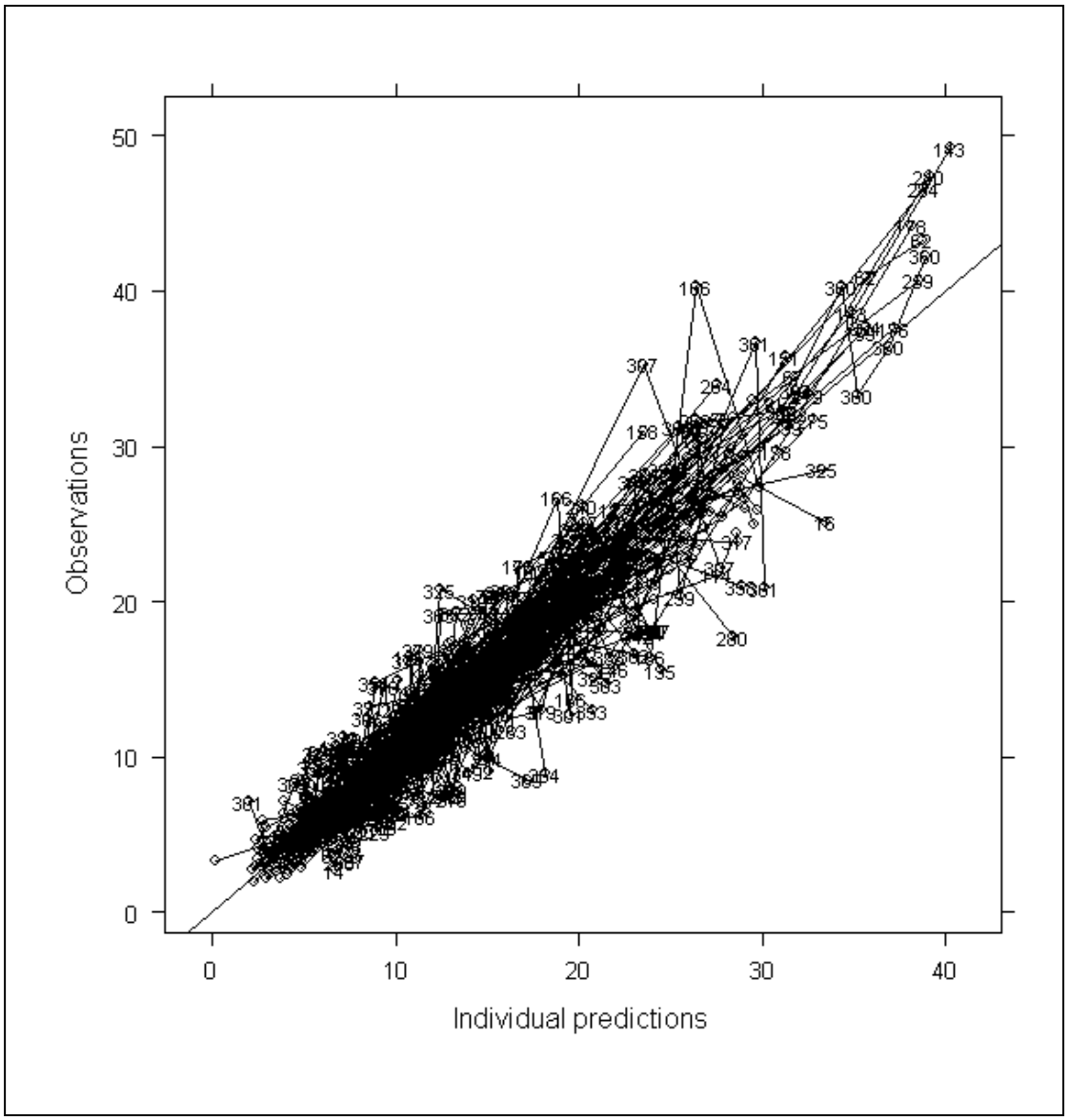

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Figure 2 a

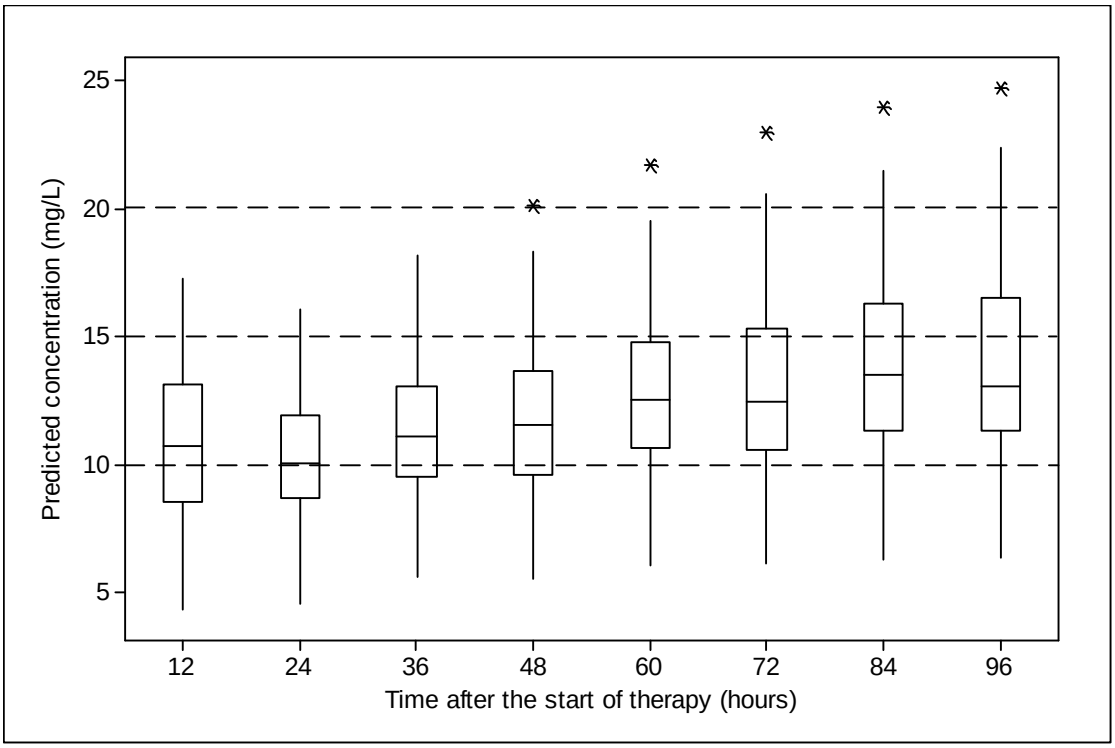

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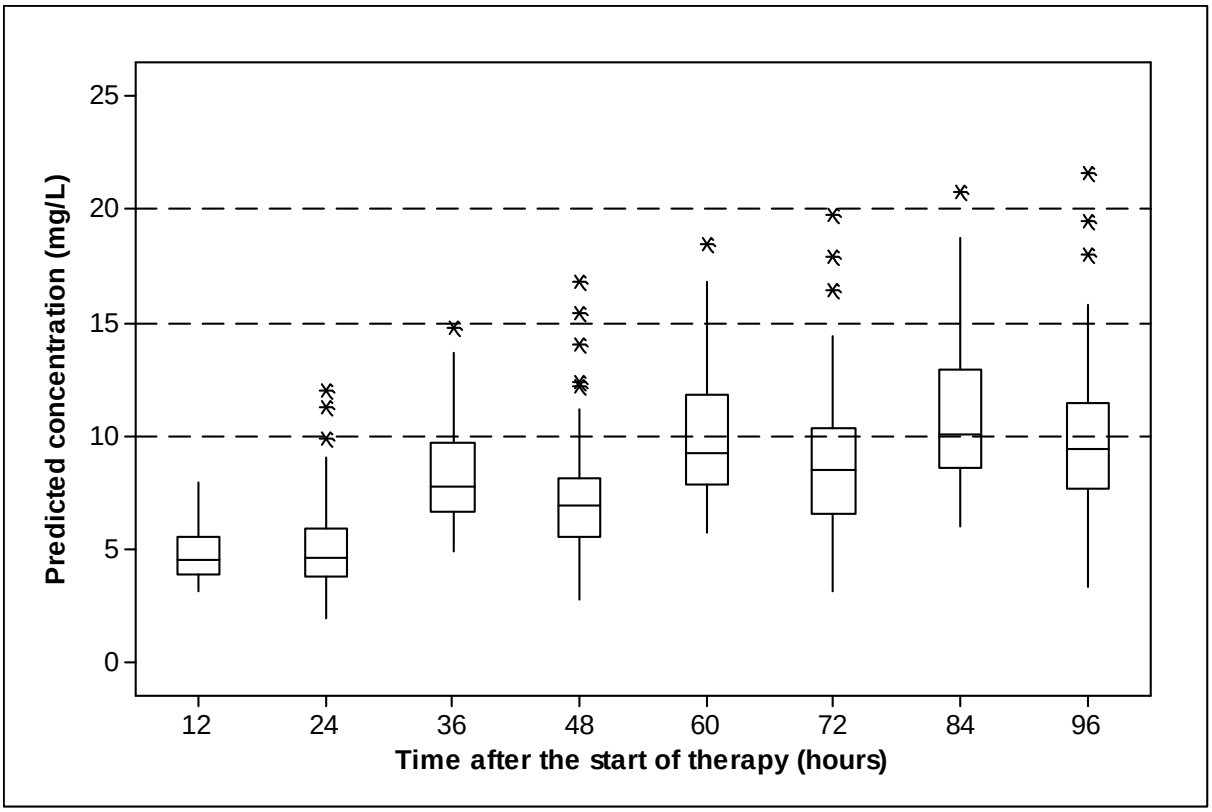
Figure 2 b



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