

Are Vancomycin Trough Concentrations Adequate for Optimal Dosing?

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The current vancomycin therapeutic guidelines recommend the use of only trough concentrations to manage the dosing of adults with *Staphylococcus aureus* infections. Both vancomycin efficacy and toxicity are likely to be related to the area under the plasma concentration-time curve (AUC). We assembled richly sampled vancomycin pharmacokinetic data from three studies comprising 47 adults with various levels of renal function. With Pmetrics, the nonparametric population modeling package for R, we compared AUCs estimated from models derived from trough-only and peak-trough depleted versions of the full data set and characterized the relationship between the vancomycin trough concentration and AUC. The trough-only and peak-trough depleted data sets underestimated the true AUCs compared to the full model by a mean (95% confidence interval) of 23% (11 to 33%; $P = 0.0001$) and 14% (7 to 19%; $P < 0.0001$), respectively. In contrast, using the full model as a Bayesian prior with trough-only data allowed 97% (93 to 102%; $P = 0.23$) accurate AUC estimation. On the basis of 5,000 profiles simulated from the full model, among adults with normal renal function and a therapeutic AUC of ≥ 400 mg · h/liter for an organism for which the vancomycin MIC is 1 mg/liter, approximately 60% are expected to have a trough concentration below the suggested minimum target of 15 mg/liter for serious infections, which could result in needlessly increased doses and a risk of toxicity. Our data indicate that adjustment of vancomycin doses on the basis of trough concentrations without a Bayesian tool results in poor achievement of maximally safe and effective drug exposures in plasma and that many adults can have an adequate vancomycin AUC with a trough concentration of < 15 mg/liter.

In 2009, the Infectious Diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists published consensus guidelines on the therapeutic monitoring of vancomycin in adults (1). The guidelines make several significant suggestions to standardize the use of vancomycin. Among these suggestions are that monitoring of pre-dose trough concentrations is “the most accurate and practical method for monitoring efficacy” and that the optimally timed sample should be obtained under steady-state conditions, just prior to the fourth dose in patients with normal renal function. The guidelines advocate abandonment of the measurement of “peak” vancomycin concentrations, which historically have been obtained up to 3 h after the end of the infusion in most cases (2–4). The rationale for abandoning peak monitoring is that there are no data correlating such peak concentrations with either efficacy or the primary adverse reaction to vancomycin, which is nephrotoxicity.

After an exhaustive review of the literature, the guideline committee concluded that available evidence suggests that the ratio of the 24-h area under the concentration-time curve (AUC_{0-24}) to the MIC (AUC/MIC ratio) drives the efficacy of vancomycin against infections with *Staphylococcus aureus*. Specifically, a total drug steady-state AUC/MIC ratio that is 400 times the MIC for the organism is the suggested target (5–8). To reconcile a trough concentration-only monitoring approach with an AUC-dependent mode of action, the committee made the assertions that vancomycin trough concentrations are a good surrogate for the AUC and that in most adult patients with normal renal function (creatinine clearance [CL_{CR}] of ≥ 100 ml/min), a steady-state trough concentration of 15 to 20 mg/liter would correlate with an AUC/MIC ratio of ≥ 400 for an organism for which the MIC is ≤ 1 mg/liter.

From an efficacy perspective, the rationale for abandoning peak monitoring in favor of a trough concentration-only approach rests on the assumptions that the trough concentration is a good surrogate for AUC and that it is simpler to obtain and measure. Therefore, the primary objective of this analysis was to explore whether these assumptions are sound by using three richly sampled vancomycin pharmacokinetic data sets (9–11).

Given the emerging data surrounding increased rates of nephrotoxicity with adherence to the dosing recommendations in the vancomycin guidelines, our second objective was to explore the relationships among trough concentrations, the AUC, and the potential rate of nephrotoxicity. Several papers have documented a higher incidence of nephrotoxicity associated with the more aggressive target trough concentrations, especially if the measured concentrations overshoot the upper target of 20 mg/liter (12–15). In contrast, a large meta-analysis suggested that a constant vancomycin concentration of 25 mg/liter through continuous infusion is less nephrotoxic than standard intermittent dosing (16). We believe that the increased toxicity associated with concentrations of > 20 mg/liter and intermittent dosing yet the reduced toxicity associated with continuously infused vancomycin at concentra-

Received 29 July 2013 Returned for modification 10 September 2013

Accepted 18 October 2013

Published ahead of print 28 October 2013

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doi:10.1128/AAC.01653-13

tions of >20 mg/liter can be explained if one attributes the risk of vancomycin toxicity to the AUC, just as for efficacy.

Finally, since comparison of measured trough concentrations to the defined ranges suggested in the guidelines requires relatively precise timing of blood sampling, e.g., just prior to the fourth dose in adults with normal renal function (1), our third objective was to test adherence to this recommendation in routine inpatient settings by using preliminary data from an ongoing clinical study of vancomycin therapeutic drug monitoring (TDM) at our institution.

MATERIALS AND METHODS

Vancomycin pharmacokinetic study data. We obtained three independent data sets from intensively sampled adults receiving vancomycin. The first data set was from a study originally published in 1990 (9). The data consisted of vancomycin dosing history, concentrations prospectively determined at frequent intervals, and patient covariates such as weight and CL_{CR} estimated by the Jelliffe formula (17), which is comparable, from a modeling perspective, to the Cockcroft-Gault formula, at least for gentamicin (18). The data were obtained from adults with prosthetic cardiac valves who each received a single dose of vancomycin prior to an outpatient dental procedure and from acutely ill adults in the cardiac intensive care unit with suspected or proven staphylococcal infections. For the outpatients, the samples were obtained 0.5 h, 1 h, at two random times, and 24 h after the start of the dose. The inpatients were sampled just before and 1, 2, 3, 8, and 12 h after a dose. Of the 19 patient records in the original study, 15 complete records were available to us: 9 of 12 in the prophylactic group and 6 of 7 in the hospitalized group.

The second data set comprised 37 adult patients requiring vancomycin therapy who had various levels of renal function estimated by the Cockcroft-Gault formula and who were enrolled in a study designed to measure the influences of age, protein binding, and renal function on vancomycin pharmacokinetics (10). Patients received a variety of doses but had 11 to 13 samples taken over a 12- to 24-h period, depending on the dosing interval, within 48 h of the initiation of therapy. Of the original 37 records, 22 were available to us.

The final cohort comprised 10 healthy adult volunteers with normal (but unspecified) CL_{CR} who were enrolled in a study to measure simultaneous plasma and alveolar endothelial lining fluid vancomycin pharmacokinetics (11). They received nine doses of vancomycin at 1,000 mg every 12 h, followed by seven blood samplings up to 24 h after the last dose.

All studies were approved by the institutional review boards (IRBs) of the respective institutions. Overall, these collected data sets represented a diverse range of adults with various levels of renal function who would be encountered routinely in clinical practice and which enabled us to build a robust and relevant model of vancomycin pharmacokinetics.

Modeling and simulation. Our overall use of the data is depicted in Fig. 1. We used the Pmetrics package version 1.1.1 (19) for R version 3.0.1 (20) to model the vancomycin pharmacokinetic data, simulate from the model, generate plots, and perform standard data summaries and statistical tests. Pmetrics is freely available from the Laboratory of Applied Pharmacokinetics and Bioinformatics (www.lapk.org).

Within Pmetrics, we used the nonparametric adaptive grid (NPAG) algorithm (19, 21, 22) to build a population pharmacokinetic model for the pooled data sets, referred to here as the data set. On the basis of the prior work of numerous authors, as reviewed by Marsot et al. (23), we used a two-compartment model for vancomycin, parameterized with linear elimination (K_e) from the central compartment with a volume (V_c) and linear transfer to (K_{cp}) and from (K_{pc}) the peripheral compartment. We estimated the values of these pharmacokinetic parameters in the population by using the full data set with all of the available information and two depleted subsets: (i) peak and trough concentrations and (ii) trough concentrations only. We defined the peak concentration as the concentration closest to 1 h after the end of the infusion and the trough concentra-

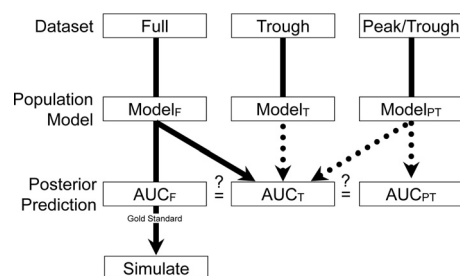


FIG 1 Use of the data. We used three versions of the data set (row 1). The full data set consisted of all 47 subjects with rich sampling for vancomycin concentration measurements. The trough concentration data set was the full data set with all nontrough concentrations, as defined in Materials and Methods, set as missing. The peak-trough concentration data set also included peak concentrations, as defined in Materials and Methods. We used each version of the data to construct population models (row 2) that differed only in the parameter value distributions based on the data. From each population model, we calculated all 47 subjects' Bayesian posterior AUCs (row 3) and compared these AUCs (=) by using the AUC_F from Model_F as the gold standard (row 3, column 1). We also used Model_F and Model_{PT} as Bayesian priors to estimate AUCs in the trough concentration data set (diagonal arrows), comparing these to the gold standard as well. Dotted arrows indicate AUCs significantly different from the AUC_F. Finally, we used Model_F for simulations.

tration as the concentration closest to 1 h before the subsequent dose. In the depleted data sets, all other concentrations were set to missing.

From the data-rich and data-depleted models, we calculated the Bayesian posterior parameter distribution for each subject and used the median of the joint distribution to calculate the vancomycin concentration-time profile at 12-min intervals and at each observation time. We compared observed and predicted concentrations and calculated the entire AUC for each subject by using the trapezoidal approximation and the predicted profile at 12-min intervals.

Assuming that the AUC estimated from the full data could be considered the "gold standard," we compared the AUCs from each depleted model to the AUCs from the full model by using a Wilcoxon signed-rank test (equivalent to a paired Student *t* test but for nonnormally distributed data) and by linear regression.

Similarly, as a way of evaluating the utility of a Bayesian approach to estimate the AUC from a limited sampling strategy, we also used the models from the full and peak-trough concentration data sets as Bayesian priors to estimate the Bayesian posterior AUCs in the trough concentration-only depleted data set.

As a second analysis, we combined the first two data sets with available CL_{CR} s (9, 10) and reestimated the population parameter value distributions as before but included CL_{CR} as a linear covariate, such that $K_e = K_{e0} \times CL_{CR}$, where K_{e0} is the elimination parameter to be estimated, normalized to CL_{CR} . We fitted model-predicted versus observed concentrations by linear regression, where model predictions were generated either by the median population parameter values or the medians of each subject's individual Bayesian posterior parameter value distributions. Once the regression of observed versus model-predicted concentrations had R^2 , slope, and intercept values close to 1, 1, and 0, respectively, we used Pmetrics and the model to simulate 5,000 concentration-time profiles each for 1,000 and 1,500 mg of vancomycin administered over 1 h every 12 h for 5 days to an adult with a CL_{CR} of 100 ml/min and calculated the resulting concentrations at 1-h intervals. We compared the simulated concentration profiles to those described in the vancomycin package insert for the same dosing regimen (<http://daily.med.nlm.nih.gov>). The mean simulated peak concentration was 22.4 mg/liter, compared to the 23 mg/liter reported in the package insert (<http://daily.med.nlm.nih.gov>). Likewise, the mean simulated plasma drug concentration at 12 h after the beginning of the infusion (C_{12}) was 9.1 mg/liter, compared with 8 mg/liter in the package insert (<http://daily.med.nlm.nih.gov>). We then estimated

TABLE 1 Characteristics of the available data sets

Data set	No. of subjects	Median (range) vancomycin dose (mg)	Total vancomycin concn ^a	Median (range) vancomycin concn/subject ^a	Median (range) CL _{CR} (ml/min)
1	15	500 (445–1,000)	124	6 (4–18)	78.0 (6.4–112.8)
2	22	850 (400–1,400)	357	14 (9–30)	56.8 (29.8–174.7)
3	10	1,000 (990–1,360)	88	9 (8–9)	Not available

^a Concentrations are in milligrams per liter of plasma.

the expected proportion of simulated profiles with a steady-state AUC_{0–24} of >400 mg · h/liter on the basis of a target AUC/MIC ratio of 400 with an MIC of 1 mg/liter and the distribution of steady-state peak and trough concentrations in that subset of profiles. In the simulated population, we defined the peak as the concentration 2 h after the beginning of a 1-h infusion, i.e., C₂, and the trough concentration as the concentration 12 h after the beginning of the infusion, i.e., C₁₂.

Regarding toxicity, we used the prior work of Lodise et al. (13), Cano et al. (12), and others to define vancomycin trough concentration intervals of <10 mg/liter, 10 to <15 mg/liter, 15 to <20 mg/liter, and ≥20 mg/liter, which are associated with an increasing risk of nephrotoxicity. We determined the AUC_{0–24} distribution in the subset of the simulated population within each trough concentration bracket and for each simulated dose. We also determined the proportion of profiles with AUC_{0–24}s of ≥1,300 mg · h/liter, which was the AUC breakpoint best associated with an increased risk of nephrotoxicity in the study by Lodise et al. (13) and ≥700 mg · h/liter, which is a more conservative breakpoint for increased risk identified by inspecting Fig. 2 in the report by Suzuki et al. (2) and by estimating the AUC_{0–24} from a continuous infusion of vancomycin with a constant concentration of 30 mg/liter, the upper end of the typical target range (30 mg/liter · 24 h ≈ 700 mg · h/liter). Meta-analysis of several studies found reduced nephrotoxicity of vancomycin continuously infused to achieve this exposure, relative to the nephrotoxicity of target serum vancomycin trough concentrations of 15 to 20 mg/liter with intermittent dosing (16).

In Pmetrics, a portion of the model misspecification (error) is regarded as associated with the quantifiable interday imprecision of the assay used to measure vancomycin concentrations. We used a fixed polynomial to calculate the standard deviation (SD) of all measured vancomycin concentrations, which was $1 + 0.1 \cdot [\text{concentration}]$. This is equivalent to an assay with a 10% coefficient of variation and an error that is more constant at very low concentrations. Pmetrics also allows a fixed gamma multiplicative error term to capture additional process noise such as errors in sample timing. We set gamma equal to 1 initially and allowed the NPAG algorithm to fit the value for the population. Therefore, in all model-building runs, each observation was weighted by $1/(\text{gamma} \cdot \text{SD}^2)$. The final-cycle gamma value was 0.96, indicating no additional process noise.

For the simulations, to avoid negative or extreme parameter values, we truncated the simulated parameters to be within the range bounded by a lower limit of zero and an upper limit of the maximum possible parameter values specified *a priori* in the NPAG algorithm fitting process. For all of the parameters, this upper limit was beyond the maximum fitted value. We also included a noise term, such that each simulated vancomycin concentration was “corrupted” by an amount randomly selected from a normal distribution with a mean of zero and a SD of $0.2 + 0.05 \cdot [\text{concentration}]$, i.e., roughly a 5% SD with increasingly larger relative noise with concentrations below the usual assay cutoff of 5 mg/liter.

Adherence to the guidelines on the timing of trough sample collection. Regarding the assumed simplicity of monitoring trough concentrations only as suggested in the guidelines (1), we analyzed preliminary data collected during the first year of an ongoing IRB-approved, NIH-funded study of vancomycin TDM at the Los Angeles County—University of Southern California Medical Center (M.N., principal investigator) registered as NCT01932034 at www.clinicaltrials.gov. In the first year of the study, we are collecting data on current vancomycin prescribing and

monitoring practice at the hospital. In the next 2 years, dosing will be guided by Bayesian feedback and AUC targets using the BestDose software (24–27) created by R. W. Jelliffe, M. N. Neely, and colleagues (formerly called MM*USCPACK and freely available at www.lapk.org). For the present analysis, from enrolled patients we prospectively recorded all vancomycin doses and measured concentrations obtained for TDM according to current practice, as well as subject demographic and clinical data. Our outcomes for this part of the analysis were the percentages of vancomycin-containing blood samples obtained within 1 or 2 h prior to the following dose (i.e., considered to be a trough), the timing of the first trough sampling with respect to the dose number, and the percentage of concentrations that were considered therapeutic according to the guidelines, on the basis of the infection, i.e., 15 to 20 mg/liter for patients with bacteremia, endocarditis, osteomyelitis, meningitis, or hospital-acquired pneumonia and 10 to 20 mg/liter for all others (1).

These subjects did not contribute to the pharmacokinetic modeling and simulation described above.

RESULTS

Combined, the three richly sampled vancomycin pharmacokinetic data sets comprised 47 adults with a total of 569 vancomycin concentrations measured after a wide range of single and multiple doses of 400 to 1,400 mg, who also had a wide range of estimated CL_{CR}s of 6.4 to 174.7 ml/min. Details of each data set are shown in Table 1. Our overall use of the data is shown in Fig. 1.

Model fit. The basic two-compartment model without any covariates was adequately able to match the observed concentrations for the full data set (Model_F). For the linear regression of Bayesian posterior individual predicted versus observed concentrations, the mean (95% confidence interval) of the intercept was 1.22 (0.53 to 1.91), where the ideal is 0; the slope was 0.956 (0.93 to 0.982), where the ideal is 1; the R^2 value was 0.902, indicating that 90.2% of the observed variability in vancomycin concentrations was explained by the parameter distributions in Model_F; the mean weighted bias (predicted minus observed) was 0.726 mg/liter; and the mean imprecision (bias-adjusted mean weighted squared error) was 9.1 mg²/liter². The ideal value of both of these is zero. Together, these regression statistics indicate that Model_F fitted the data well. The mean (SD) parameter values in Model_F were as follows: K_e , 0.30 (0.19) h^{−1}; V_c , 14.8 (7.9) liters; K_{CP} , 1.13 (0.78) h^{−1}; K_{PC} , 0.66 (0.94) h^{−1}. This corresponds to a clearance of 3.0 (2.0) liters/h, which, not surprisingly, given the variable renal function, ranged from 0.4 to 9.6 liters/h. These values are in agreement with the package insert (<http://dailymed.nlm.nih.gov>), assuming an adult body weight of 75 kg.

Vancomycin AUC. The cumulative subject vancomycin AUCs based on the full data set (AUC_F), from the first dose until the last measured vancomycin concentration, had a median (range) of 1,857 (202 to 6,963) mg · h/liter, over a time interval of 120.2 (11.9 to 362.4) h. We divided each subject's cumulative AUC_F by the total time in hours and multiplied the result by 24 to estimate the

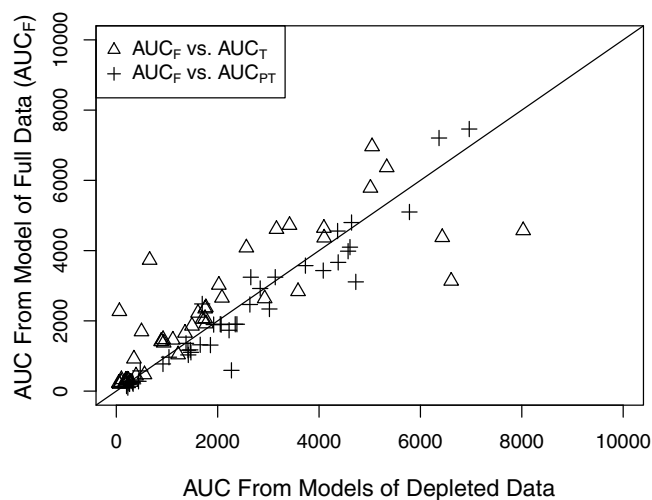


FIG 2 Linear regression of AUCs predicted from full data (AUC_F) versus depleted data. Data were depleted to trough concentrations only (AUC_T , triangles) or peak and trough concentrations (AUC_{PT} , crosses). The solid line is the line of identity, i.e., perfect agreement.

daily AUC_F , with a median (range) of 445.2 (28.3 to 7,172) $\text{mg} \cdot \text{h}/\text{liter}$.

By the Wilcoxon signed-rank test (equivalent to a paired Student t test but for nonnormally distributed data), the AUCs estimated from both the peak-trough (AUC_{PT}) and trough-only (AUC_T) data sets were significantly lower than those from the full data set. The median AUC_F -minus- AUC_{PT} difference was 159.3 (95% confidence interval [CI], 63.6 to 284.6) ($P = 0.0009$), while the mean (95% CI) AUC_{PT}/AUC_F ratio was 0.86 (0.81 to 0.93) ($P < 0.0001$). The median (95% CI) AUC_F -minus- AUC_T difference was 341.9 (189.8 to 553.4) ($P = 0.0001$). The mean (95% CI) AUC_T/AUC_F ratio was 0.78 (0.67 to 0.89) ($P = 0.0002$). Therefore, both Model_{PT} and Model_T underpredicted the AUC relative to Model_F .

As shown in Fig. 2, by linear regression, AUC_{PT} predicted the AUC_F with less variability, as indicated by an R^2 value and median (range) residuals of 0.94 and -139.6 (-958.7 to $1,468.0$), than did AUC_T , with an R^2 value and median residuals of 0.70 and -97.1 ($-2,625.0$ to $2,478.0$).

When using Model_F as a Bayesian prior to estimate the AUC from the trough-only depleted data set (AUC_{F-T}) by the Wilcoxon signed-rank test, the median (95% CI) AUC_F -minus- AUC_{F-T} difference was 23.1 (-21.8 to 71.7) ($P = 0.28$). The mean (95% CI) AUC_{F-T}/AUC_F ratio was 0.97 (0.93 to 1.02) ($P = 0.23$). When using Model_{PT} as a Bayesian prior to estimate the AUC from the trough-only depleted data set (AUC_{PT-T}), the median (95% CI) AUC_F -minus- AUC_{PT-T} difference was 229.1 (99.9 to 352.7) ($P < 0.0001$). The AUC_{PT-T}/AUC_F ratio was 0.85 (0.79 to 0.91) ($P < 0.0001$). Therefore, Model_F served as a good prior that was able to accurately estimate the AUC even from trough-only data, while using Model_{PT} as a prior for trough-only data underestimated the AUC.

Simulations. The model with CL_{CR} as a covariate affecting vancomycin elimination fitted the pooled data from sets 1 and 2 with a bias of only 0.25 mg/liter and an imprecision of 6.3 $\text{mg}^2/\text{liter}^2$ ($\text{Model}_{CL_{CR}}$). Data set 3 was missing CL_{CR} information, and it was not included in this part of the analysis.

The results for the 5,000 profiles simulated with the 1,000-mg dose and the 5,000 profiles simulated with the 1,500-mg dose are shown in Table 2. Not surprisingly, nearly three times as many profiles with the higher dose had a steady-state AUC_{0-24} of ≥ 400 $\text{mg} \cdot \text{h}/\text{liter}$, the target for an organism for which the MIC is 1 mg/liter . However, the higher dose was also associated with the potentially toxic AUC_{0-24} of ≥ 700 $\text{mg} \cdot \text{h}/\text{liter}$ in nearly six times as many profiles as with the lower dose. Among those with an AUC_{0-24} of ≥ 400 or ≥ 700 $\text{mg} \cdot \text{h}/\text{liter}$, the distributions of C_2 (peak) and C_{12} (trough) were broad. The range of C_{12} s is also shown in Fig. 3. Conversely, within those profiles with a C_{12} of ≥ 20 mg/liter , the range of AUC_{0-24} values was also broad, as shown in Table 2.

Adherence to routine monitoring guidelines. At our institution, the routine vancomycin monitoring point is a trough prior to the fourth dose. From the ongoing clinical study of current vancomycin monitoring practice at our institution, of 36 enrolled subjects (33 adults, 3 children) with at least one available measured vancomycin concentration in the first week, only seven (19%) of the first samples that were followed by an additional dose were obtained within the hour before that dose; i.e., 81% were not actually trough concentrations. Relaxing the time interval to 2 h before the next dose captured a total of 14 (39%) samples. The median (range) trough concentration of the 14 samples was 8.0 (1.1 to 17.5) mg/liter . Of the seven obtained within an hour before the next dose, five (71%) were not optimally therapeutic according to the guidelines, and this percentage was the same when all 14 samples obtained within 2 h of the next dose were included. All of these “nontherapeutic” trough concentrations were below the recommended target. The first vancomycin concentration was measured after a median of four doses, in accordance with the published and local guidelines; however, only 42% actually were measured after this dose. Another 28% were measured after doses 1 to 3, leaving 30% measured after dose 5 or later and in two subjects not until dose 8. The median time to the first concentration was 35 h after the first dose (range, 8.0 to 117.0 h). The median dose was 13.4 mg/kg (range, 7.7 to 35.7 mg/kg) with a median daily dose of 28.2 mg/kg (range, 10.0 to 74.3 mg/kg). Only 2 (5%) of the 36 subjects were considered to have nephrotoxicity associated with vancomycin therapy, defined as a rise in serum creatinine of $>50\%$ or >0.5 mg/dl from the baseline. These two patients had a mean vancomycin trough concentration of 10.5 mg/liter versus 14.8 mg/liter in the patients without toxicity ($P = 0.21$).

DISCUSSION

To our knowledge, this is the largest population pharmacokinetic model of vancomycin in adults with prospectively collected, intensively scheduled samples, i.e., more than peak-trough or trough-only sampling obtained from routine, clinically obtained TDM data. In combination with the diversity of the vancomycin doses and patient CL_{CR} s, these data permit us to carefully explore vancomycin dosing and exposures in adults.

From our analysis, we are able to draw several important conclusions. First, on the basis of our simulations, even in an ideal population of adults with normal renal function who get the same dosing regimen, vancomycin AUC values can vary as much as 30-fold between patients, with associated variability in peak and trough concentrations. This interpatient variability, in light of substantial evidence of concentration-response relationships

TABLE 2 Vancomycin exposures of simulated profiles with two doses given by 1-h intravenous infusion every 12 h

Parameter	Value achieved with dose of:	
	1,000 mg	1,500 mg
Median (range) AUC ₀₋₂₄ (mg · h/liter)	343.1 (72.5–2,194.0)	514.5 (109.0–3,291.0)
% (no.) of patients with AUC ₀₋₂₄ (mg · h/liter) of:		
≥400	28.7 (1,435)	80.1 (4,005)
≥700	2.7 (136)	15.7 (787)
≥1,300	0.02 (1)	0.38 (19)
Median (range) AUC ₀₋₂₄ of those with trough concn >20 mg/liter	602.0 (225.7–2,194.0)	728.6 (264.8–3,291.0)
% (no.) with trough concn of >20 mg/liter and AUC ₀₋₂₄ (mg · h/liter) of:		
<400	14 (52)	3 (29)
400–700	61 (229)	41 (389)
≥700	26 (97)	56 (526)
Median (range) concn (mg/liter) of those with AUC ₀₋₂₄ of ≥400 mg · h/liter		
Peak	36.0 (22.6–132.7)	42.1 (22.8–199.1)
Trough	13.3 (1.9–72.6)	11.9 (0.69–108.8)
% of patients with trough concn (mg/liter) of:		
<10	32	38
10 to <15	27	26
15 to <20	18	14
≥20	23	23
Median (range) concn (mg/liter) of those with AUC ₀₋₂₄ of ≥700 mg · h/liter		
Peak	56.9 (42.9 to 132.7)	62.3 (40.2 to 199.1)
Trough	26.2 (5.3–72.6)	25.5 (4.7–108.8)
% (no.) of patients with trough concn (mg/liter) of:		
<10	10 (14)	5 (40)
10 to <15	10 (13)	15 (115)
15 to <20	9 (12)	13 (106)
≥20	71 (97)	67 (526)

(6–8, 14), is strong justification for ongoing vancomycin TDM, especially since exposure among patients with various degrees of renal function will be even more unpredictable from a dose.

Second, a traditional approach to TDM by comparing vancomycin trough concentrations to a predefined range is a very poor surrogate for estimation of the AUC and overall vancomycin exposure. On average, this will underestimate the true AUC by about 25%, and there is such tremendous interpatient variability that the estimated AUC of any one patient will be unreliable and can be even more inaccurate.

Inclusion of peak concentrations in vancomycin TDM strategies was standard practice until many studies, most recently one by Suzuki et al. (2), showed that there was no relationship between peaks and either efficacy or toxicity. Given the high variability of peak concentrations even within subsets of simulated profiles with AUCs above thresholds, e.g., 400 or 700 mg · h/liter, it is not surprising that relationships between peaks and outcomes cannot be demonstrated. However, without the availability of a Bayesian feedback tool, the inclusion of a peak concentration may improve vancomycin AUC estimates.

When a model based on richly sampled vancomycin data is used as a Bayesian prior, even trough-only data can be used to generate accurate and reliable AUC estimates that deviate from the truth by only 3%, on average. In contrast, our model based on

peak and trough concentrations was worse at predicting the true AUC from vancomycin trough concentrations. This is an extremely important point, since nearly all of the published vancomycin population models are based on such limited peak-trough sampling, especially in pediatric populations (23). However, it is possible that if two more informative, optimally sampled points after the end of the infusion are selected, then such a model may serve as a better Bayesian prior.

Third, we propose that if vancomycin toxicity is most strongly linked to the AUC, then a steady-state 24-h AUC of 700 mg · h/liter represents a conservative upper level of safe vancomycin exposure with a minimal risk of nephrotoxicity, subject to the needs of individual patients. Above this threshold, we believe that the risk of toxicity will increase more rapidly. This is consistent with observations, including those in the guidelines (1), that for organisms for which the vancomycin MIC is ≥2 mg/liter, i.e., at an AUC of 800 mg · h/liter when maintaining a 400:1 ratio, toxicity begins to increase noticeably. We also believe that focusing on the AUC as the correct marker of toxicity risk is the explanation for the superficially contradictory observations that trough concentrations of >20 mg/liter are associated with increased nephrotoxicity when vancomycin is dosed intermittently (12, 13, 15, 28, 29), while constant concentrations of 20 to 30 mg/liter with continuous vancomycin infusions may be associated with less nephrotoxicity than

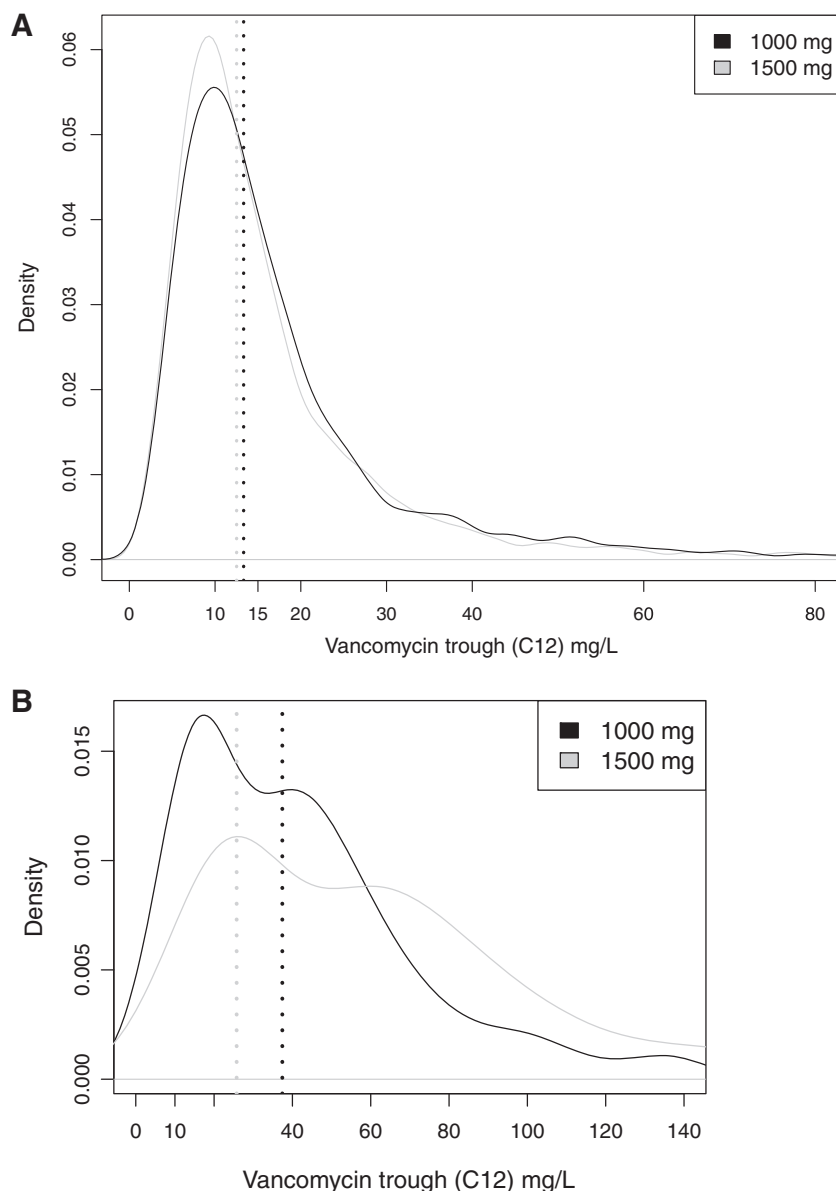


FIG 3 Distribution of steady-state vancomycin trough concentrations among 5,000 simulated adult patients who received 1,000 mg (black) or 1,500 mg (gray) of vancomycin by a 1-h infusion every 12 h and who had a 24-h AUC of ≥ 400 mg·h/liter (A) or ≥ 700 mg·h/liter (B). Each panel shows the probability densities of the trough concentration distributions, which are normalized to the number of sample trough concentrations. The vertical dotted lines are the median trough concentrations for the two doses. Note that the median trough concentration in both panels is higher for the lower dose (1,000 mg) because lower clearance is required to achieve a given AUC for a lower dose ($\text{AUC} = \text{Dose}/\text{Clearance}$), which results in higher trough concentrations. The effect is more pronounced at the higher AUC target in panel B.

intermittent dosing (16) or at least do not appear to be more toxic. Basic pharmacokinetic equations confirm that the smallest daily dose required to maintain the concentration above a minimum target is achieved by continuous infusion and that for the same minimum target, the daily dose divided into increasingly long intervals must be correspondingly larger, as must the daily AUC. We are not necessarily advocating continuous infusions under all circumstances, but we are using all available information to support our hypothesis about the importance of the vancomycin AUC as a driver of both efficacy and toxicity.

Obviously, not all patients with intermittent vancomycin dosing and trough concentrations of ≥ 20 mg/liter develop nephro-

toxicity. Of our simulated patients who had trough concentrations of >20 mg/liter, about 25 to 55% had AUCs of ≥ 700 mg·h/liter, depending on the dose. This probability of possibly toxic vancomycin exposure agrees well with four clinical studies that found early vancomycin trough concentrations of >20 mg/liter to be associated with subsequent nephrotoxicity in approximately 25 to 40% of patients (12, 13, 28, 29). The study by Lodise et al. (13) was the only one that attempted to directly examine the relationship between AUC and nephrotoxicity, and they found 7 (26%) subjects with nephrotoxicity among 27 with a vancomycin AUC of $>1,300$ mg·h/liter. There is little doubt that the risk of nephrotoxicity is substantial at that exposure level, and our proposed

threshold of 700 mg · h/liter is safely below this unacceptably high rate and high enough to permit the treatment of infections with organisms for which the MIC is ≤ 1.5 mg/liter. At least as high as 900 mg · h/liter, the increase in the risk of nephrotoxicity is likely small (13), likely permitting safe treatment of organisms for which the MIC is 2 mg/liter in many patients. Of course, prospective validation of our proposed target would be desirable.

The fourth important conclusion from our data and simulations is that in addition to the variability in AUCs, trough concentrations differ greatly between patients, even among adults who have normal renal function and who are getting the same dose. This means that 50 to 60% of adults who have an AUC of ≥ 400 mg · h/liter, which may be adequate to treat an infecting organism for which the MIC was 1 mg/liter, are not expected to have a trough concentration of >15 mg/liter. Increasing those patients' dose to achieve a trough concentration of >15 mg/liter will needlessly raise the AUC and increase the chance of renal injury. This dissociation between the therapeutic AUC and trough concentrations of <15 mg/liter or even <10 mg/liter has also been demonstrated in children (30, 31).

Finally, on the basis of our experience with vancomycin TDM and that of others (32), comparing trough concentrations to a predefined range is an especially poor approach since many concentrations are not obtained at the appropriate time. This makes their interpretation inaccurate, with correspondingly inaccurate dose changes. It is extremely difficult in a busy clinical setting to obtain reliably timed samples. Furthermore, even among the appropriately timed samples in our data, the majority of the concentrations were below the target range. This can mean dose adjustment and repeated sampling at the new steady state, potentially resulting in days of suboptimal exposure. The low 5% incidence of nephrotoxicity in our patient population is consistent with the lower vancomycin concentrations that we observed and those observed in other studies (12, 13).

The guidelines for vancomycin TDM are clear in their language about the importance of the AUC, at least for efficacy. The experts who wrote the guidelines are equally clear that they view trough concentration as a surrogate for the AUC, although we have shown that it is a poor one. In the past, the AUC has been cumbersome to calculate and use, especially compared to the ease of comparing a single trough concentration to a range. However, it is time to recognize that we can easily manage AUC-guided dosing with numerous computer programs, such as BestDose, (24–27). BestDose has been used successfully to target vancomycin trough concentrations (33) and also reports AUCs. A version of BestDose that includes our model of vancomycin is freely available at the Laboratory of Applied Pharmacokinetics and Bioinformatics website (www.lapk.org). These kinds of Bayesian tools offer numerous advantages, such as using samples obtained at any time, even over numerous dosing intervals. Samples do not have to be taken under steady-state conditions, although predictions of the entire steady-state concentration-time profile or specific targets at times other than those sampled may be more accurate with steady-state samples, depending on the tool (34). Furthermore, we do not have to be wedded to trough concentrations. One study determined that there were several sets of optimal sampling times using a D-optimal approach (35) that estimated vancomycin pharmacokinetic parameters in premature infants equally well (36), and it is possible that these times may be different in other populations.

All of these advantages are attractive given the unpredictable nature of daily patient care activities.

For centers without access to experts who can perform Bayesian analysis, one might consider estimating the AUC by a variety of other methods, typically based on nomograms or other software methods, as recently catalogued by Avent et al. (37). However, nomograms and dosing algorithms are less flexible than Bayesian methods with respect to sample times, typically assume that the patient is average with respect to vancomycin pharmacokinetic behavior, and consider only concentrations obtained within a single dosing interval.

Limitations of our study arise from conclusions based on a group of only 47 patients. We were not able to locate additional richly sampled data sets to use, nor were we able to find any on children. Future studies must address this paucity of richly sampled vancomycin pharmacokinetic data in all patient populations. For 21st century vancomycin management, optimally sampled, AUC-guided dosing with computerized decision support should be more widely used and evaluated, as has been recommended by others (37). While there are barriers to the implementation of such a strategy in hospitals and clinics (24), these are largely logistic and educational, not technological, and can be overcome (38).

ACKNOWLEDGMENTS

We thank all of the study participants and other members of LAPKB who did not directly contribute to this project but whose tireless work keeps Pmetrics and BestDose running, including Michael van Guilder, Alan Schumitzky, David Bayard, Tatiana Tatarinova, Jay Bartroff, Walter Yamada, and Alona Chubatiuk.

M.N. performed the modeling, simulation, and statistical analyses and wrote the manuscript. G.Y. and B.J. recruited all of the patients into the present clinical study and collected all of the data. R.J., G.D., K.R., and T.L. designed and conducted the vancomycin pharmacokinetic studies and analyzed the data, advised on the analysis of the data in this report, and edited the manuscript.

M.N. is a founder of Applied Pharmacometrics, Inc., which is developing the BestDose software for commercial distribution. He and R.J. provide scientific advice to the company but do not receive any financial compensation. M.N. is also the principal investigator of the Laboratory of Applied Pharmacokinetics and Bioinformatics, which produces Pmetrics as a free research tool and developed the algorithms powering BestDose (both available at <http://www.lapk.org>).

This work was supported by NIH grants GM068968 and HD070886.

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