Comparison of the Area Under the Curve for Vancomycin Estimated Using Compartmental and Noncompartmental Methods in Adult Patients With Normal Renal Function

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Background: Vancomycin pharmacokinetics are best described using a 2-compartment model. However, 1-compartment population models are commonly used as the basis for dose prediction software. Therefore, the validity of using a 1-compartment model to guide vancomycin drug dosing was examined.

Methods: Published plasma concentration–time data from adult subjects (n = 30) with stable renal function administered a single intravenous infusion of vancomycin were extracted from previous studies. The vancomycin area under the curve ($AUC_{0-\infty}$) was calculated for each subject using noncompartmental methods (AUC_{NCA}) and by fitting 1- (AUC_{1CMT}), 2- (AUC_{2CMT}), and 3- (AUC_{3CMT}) compartment infusion models. The optimal model fit was determined using the Akaike information criterion and visual inspection of the residual plots. The individual compartmental $AUC_{0-\infty}$ values from the 1- and 2-compartment models were compared with AUC_{NCA} values using one-way repeated measures analysis of variance.

Results: The mean (±SD) AUC estimates were similar for the different methods: AUC_{NCA} 180 ± 86 mg·h/L, AUC_{1CMT} 167 ± 79 mg·h/L, and AUC_{2CMT} 183 ± 88 mg·h/L. Despite the overlapping AUC values, AUC_{2CMT} and AUC_{NCA} were significantly greater than AUC_{1CMT} ($P < 0.05$). The 3-compartment model was excluded from the analysis because of the failure to converge in some instances.

Conclusions: Dose prediction software using a 1-compartment model as the basis for Bayesian forecasting underestimates drug exposure (estimated as the AUC) by less than 10%. This is unlikely to be clinically significant with respect to dose adjustment. Therefore, a 1-compartment model may be sufficient to guide vancomycin dosing in adult patients with stable renal function.

Key Words: therapeutic drug monitoring, vancomycin, antibiotics, pharmacokinetics

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BACKGROUND

Intravenous (IV) vancomycin is the first-line treatment for invasive infections due to methicillin-resistant *Staphylococcus aureus*.[1] Current guidelines recommend that monitoring vancomycin drug exposure, as assessed by the area under the plasma concentration–time curve (AUC), rather than steady-state trough concentrations, is the best pharmacokinetic (PK) predictor of therapeutic outcomes.[2–4] A ratio of AUC_{0-24} to minimum inhibitory concentration greater than 400 is accepted as the optimal target for clinical efficacy.[2] However, in the absence of methods to calculate AUC using sparse vancomycin concentration data, current therapeutic drug monitoring (TDM) of vancomycin is often guided by the use of trough concentration targets (15–20 mg/L). Recently, computerized Bayesian forecasting programs have been developed to estimate patient-specific AUC with limited vancomycin concentration sampling.[5] Integrated Bayesian-TDM-guided dosing based on vancomycin AUC would require fewer blood samples, enhance the flexibility of sample collection, increase the accomplishment of therapeutic targets, and, therefore, optimize the likelihood of increased treatment efficacy and reduced drug toxicity, compared with the current trough-based TDM approach.[6,7]

When applied to predictions of drug dosage, the Bayesian method integrates a population PK model with individual data to estimate PK parameters for each subject.[8] However, before implementation in clinical practice, the suitability of population PK models used by different Bayesian forecasting programs requires assessment. The accuracy of Bayesian forecasting programs in predicting AUC is largely determined by the robustness and generalizability of the population model used. A major consideration is the number of compartments included in the population model to describe the PK of drugs. Vancomycin PK has been described using 1-, 2-, and 3-compartment models.[9,10] A number of commercial Bayesian forecasting programs

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TABLE 1. Overview of Studies Reporting Individual PK Parameters After a Single IV Dose of Vancomycin

	Blouin et al[10]	Hurst et al[12]	Kergueris et al[13]
Study location	USA	USA	France
Total subjects (n)	10	11	10
Study population	Four normal and 6 morbidly obese subjects. All morbidly obese (BMI > 40 kg/m^2) subjects were 3–4 h postgastric bypass surgery	Ambulatory subjects with prosthetic cardiac valves receiving vancomycin prophylaxis before dental procedures	Neutropenic subjects with hematological malignancies
Clinical signs or symptoms of infection	No	No	Yes, presumed or documented gram-positive bacterial infection
Renal function exclusion criteria	Subjects with CrCL < 90 mL/min/1.73 m^2	Not reported	Subjects with CrCL < 70 mL/min/1.73 m^2
Type of CrCL reported	Measured CrCL	Measured CrCL	Measured CrCL
Hepatic/cardiac function exclusion criteria	Not reported	Not reported	Subjects with hepatic or severe cardiac insufficiency
Vancomycin dosage	1 g infused over 40 min	1 g (or 15 mg/kg if <50 kg) infused over 1 h	1 g infused over 1 h
Frequency of blood sample collection	21 samples collected at 0 h, midpoint of infusion, and at the end of infusion, 5, 10, 20, 30, 45 min, and 1, 1.5, 2, 3, 4,5, 6, 7, 8, 10, 12, 16, and 24 h after infusion	Five samples collected 0.5 h, 1 h, immediately before dental procedure, immediately after dental procedure, 24 h after infusion	Eight samples collected between 15 min and 11 h after infusion
Vancomycin assay	Radioimmunoassay (monitor science)	Fluorescence polarization immunoassay (TDx, Abbott Laboratories, North Chicago)	Immunoassay (TDx, ABBOTT)
Vancomycin assay lower limit of detection	0.5 mcg/mL	Not reported	Not reported
PK analysis program	SAAM 23	PC-Adapt/USC PACK PC	USC PC PACK
Structural model	3-Compartment, weighted ($1/C_{observed}^2$) nonlinear least squares regression	2-Compartment, weighted nonlinear least-squares regression	2-Compartment
Concentration data reported?	Yes	No, only detailed PK parameters reported	No, only detailed PK parameters reported
AUC reported?	No	No	No

AUC, area under the time course of plasma concentrations.

use either 1- or 2-compartment models. However, in adults, it is generally accepted that vancomycin PK is best described by a 2-compartment model.[9,11] Bayesian forecasting programs that use a 1-compartment model do so for the sake of simplicity. It is unclear whether total exposure (AUC) to vancomycin derived from a 1-compartment, rather than a 2-compartment model, is appropriate for predicting drug doses using Bayesian forecasting. Indeed, data comparing AUC calculated using 1-, 2-, and 3-compartment models is sparse. Therefore, this study aimed to compare the $AUC_{0-\infty}$ calculated using 1-, 2-, and 3-compartment models. We hypothesized that a 1-compartmental model would sufficiently describe vancomycin AUC in adult patients with stable renal function, even though the 2-compartment model is best fit to adequately inform vancomycin dosing decisions.

METHODS

Subjects

Studies reporting intensive concentration–time data from subjects administered a single infusion (1000 or 15 mg/kg if weight <50 kg) of vancomycin were identified and data were extracted[10,12,13] (see **Text**, **Supplemental Digital Content 1**, http://links.lww.com/TDM/A363). The details of these studies are outlined in Table 1.

Pharmacokinetic Analysis

Individual vancomycin PK parameters were determined using the PKSolver Version 2.0 add-in program for Microsoft Excel.[14] The plasma vancomycin concentrations for all subjects were fitted to a noncompartmental IV infusion model and the $AUC_{0-\infty}$ was calculated for each subject by the linear ascending, log-linear descending trapezoidal approach ("AUC_{NCA}"). PK parameters were determined as follows: terminal rate constant (λ_z), taken as the slope of the terminal phase of the log-linear concentration–time profile; and area under the concentration–time profile extrapolated to infinity ($AUC_{0-\infty}$), calculated as $AUC_{last} + C_{last}/\lambda_z$, where C_{last} is the last quantifiable concentration of the concentration–time profile. AUC_{NCA} was calculated to serve as a comparator for the AUC values based on compartmental methods.

Plasma vancomycin concentrations for all subjects were subsequently fitted using a compartmental modelling approach (weighting factor of $1/C_{observed}^2$). Three (1-, 2-, and 3-compartment) structural models were assessed to

TABLE 2. Characteristics of Subjects Receiving a Single Dose of Vancomycin (n = 30)

	Blouin et al (Morbidly Obese)[10]	Blouin et al (Nonmorbidly Obese)[10]	Hurst et al[12]	Kergueris et al[13]	All Studies
Total subjects (%)	6 (25.0)	4 (13.3)	11 (36.7)	9 (30.0)	30 (100)
Male, % (n)	33 (2)	100 (4)	55 (6)	44 (4)	53 (16)
Age (yr)	31 (3.7)	28 (2.4)	54 (12.4)	38 (8.5)	41 (13.6)
Weight (kg)	166 (44.0)	75 (10.1)	64 (20.3)	66 (10.6)	86 (46.5)
Height (cm)	171 (11.6)	178 (4.4)	164 (10.6)	167 (10.5)	168 (10.7)
BMI (kg/m^2)	56.0 (10.2)	23.6 (2.0)	23.3 (6.5)	23.4 (1.9)	29.9 (14.5)
Creatinine clearance (mL/min)*	180 (44)	138 (28)	72 (28)	141 (47)	123 (55)
Creatinine clearance (mL/min/1.73 m^2)†	249 (111)	155 (44)	75 (24)	139 (37)	139 (84)

Data presented as mean (SD).
*Creatinine clearance (measured from a urine and serum collection).
†Indexed to body surface area using the Dubois and Dubois method.[16]

determine whether 2- or 3-compartment models improved the accuracy of the AUC estimated using a 1- compartment model. Individual time courses of plasma concentrations and subsequently, the individual $AUC_{0-\infty}$ values for the 1-, 2-, and 3-compartment models were each calculated using equivalent standard PK equations appropriate for vancomycin administered as an infusion injection.[15] $AUC_{0-\infty}$ values for the 1-, 2-, and 3-compartment models were calculated as AUC_{1CMT}, AUC_{2CMT}, and AUC_{3CMT}, respectively. The optimal model fits for each subject were determined from the Akaike criterion, and visual inspection of the fit of the time courses of plasma concentration residual plots.

Statistical Analysis

$AUC_{0-\infty}$ values obtained using the noncompartmental (AUC_{NCA}) and compartmental approaches (AUC_{1CMT}, AUC_{2CMT}) were compared using a one-way repeated measures analysis of variance. Comparisons of means for *post-hoc* analysis were conducted by Tukey contrasts with Bonferroni correction.

To assess whether a 1-compartmental model could sufficiently describe vancomycin AUC compared to a "gold-standard" 2-compartment AUC, we adopted a maximum acceptable imprecision for AUC_{1CMT} versus AUC_{2CMT} of 20%, based on the following reasoning: At our institution, AUC-based monitoring for vancomycin is guided by a conservative target of AUC/minimum inhibitory concentration of 400–600 mg·h/L. The 1-compartment model will lead to under- rather than over-prediction compared with a 2-compartmental approach. Estimated AUCs just below 400 mg·h/L are unlikely to lead to toxicity, given the wide therapeutic range. Estimated AUCs just above 600 mg·h/L may lead to unnecessary drug exposure. Accepting an AUC upper limit of 700 mg·h/L for nephrotoxicity, the maximum acceptable imprecision for $AUC_{1\text{-}CMT}$ versus $AUC_{2\text{-}CMT}$ is defined as: (700–600)/600 = 17% ≅ 20%.

Linear regression for body mass index (BMI) versus absolute prediction error for AUC_{1CMT} (measured by AUC_{1CMT} minus AUC_{2CMT}, in mg·h/L) was used to assess whether the accuracy of AUC_{1CMT} values decreases compared with AUC_{2CMT} values with increasing BMI. Statistical analyses were performed using R version 3.5.0.

RESULTS

Subject Characteristics

Data reported in the literature comprised a richly sampled cohort of 30 subjects.[10,12,13] One subject from

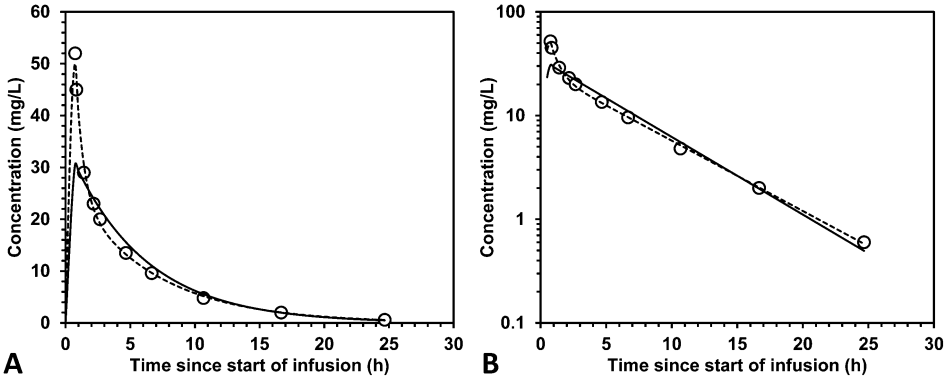

FIGURE 1. Vancomycin concentration time profiles as described by the 1- and 2-compartment models, after infusion: (A) linear axes, (B) logarithmic y axis in a representative subject (Blouin Subject N1). Open circles represent the observed vancomycin concentrations. Solid lines represent fits from the 1-compartment model and the dashed lines represent fits from the 2-compartment model. On average, the distribution phase of the 2-compartment concentration time profile contributed 22.6% (SD ± 9.7%) of the total AUC.

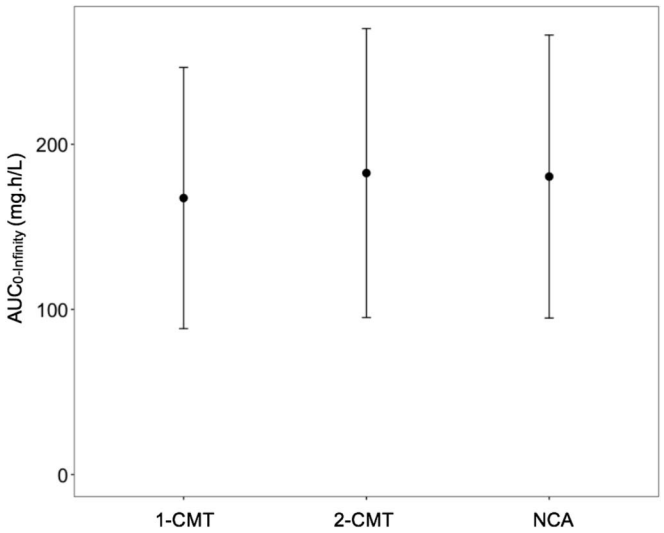

FIGURE 2. Vancomycin drug exposure ($AUC_{0-\infty}$) after a single dose in adults (n = 30) calculated from 1- and 2- compartment (1-CMT and 2-CMT, respectively) and noncompartment (NCA) analyses. Data presented are the mean and SD.

Kergueris et al[13] was excluded because of insufficient data. Subject demographics are provided in Table 2. Overall, the mean (±SD) age was 41 ± 13.6 years, and 53% were men. The mean body weight was 86 ± 46.5 kg, and 20% of subjects were morbidly obese (BMI > 40 kg/m^2). Mean measured creatinine clearance (CrCL) was 140 ± 84 mL/min/1.73 m^2 and when adjusted, and indexed to body surface area using the Dubois and Dubois method,[16] the mean estimated CrCL was 123 ± 55 mL/min.

Compartmental Structural Model Fits for Vancomycin

The individual vancomycin concentration time data were satisfactorily fitted using both the 1- and 2- compartment models (Fig. 1). As anticipated, based on the Akaike criterion and residual plots, the fit of the data to the 2-compartment model was superior to that of the 1-compartment model in the distribution phase, because fitting to 1-compartment does not include a distribution phase. The 3-compartment model only converged in 73% of cases and was therefore not considered further. As shown by the SD, there was considerable variation in the AUC values determined from the 3 methods.

Based on the Akaike criterion, the 2-compartment model was superior to the 1-compartment model in patients with and without morbid obesity. The 2-compartment model also had a lower Akaike criterion than the 3-compartment model for most subjects for which the 3-compartment model converged.

Comparison of Vancomycin Drug Exposure

Repeated measures analysis of variance indicated that the mean AUC values of the 3 methods (NCA, 1-compartment, and 2-compartment approaches) were statistically different ($P < 0.001$); however, the difference was very small and not clinically significant (Fig. 2). Mauchly test of sphericity indicated that the assumption of sphericity had been violated ($P < 0.001$) and therefore, a Greenhouse–Geisser correction was used. On average, AUC_{2CMT} was larger than AUC_{1CMT} ($P < 0.001$; Table 3). A *post-hoc* power analysis indicated that with 30 subjects and a correlation of 0.991 between AUC_{1CMT} and AUC_{2CMT}, statistical power exceeded 99% to detect a 20% difference in AUC_{1CMT} and AUC_{2CMT} at a 2-sided significance level of 0.05.

The mean (±SD) AUC from the 2-compartmental approach was 183 ± 88 mg·h/L and the corresponding AUC from the 1-compartment model was 167 ± 79 mg·h/L. Although the difference was statistically significant, clinically, the difference in AUC values (8.3%) was smaller than the 20% threshold for maximum acceptable imprecision (Table 3). The mean AUC value estimated by the noncompartmental method (180 ± 86 mg·h/L) was also significantly larger than that from the 1-compartmental model. Again, the clinical difference as small (7.2%) although statistically significant. The AUC_{NCA} and AUC_{2CMT} values were similar ($P = 0.85$) (Table 3).

Effect of Body Weight on Estimates of Vancomycin Drug Exposure

Overall, there was a weak positive linear correlation between BMI and absolute prediction error for AUC_{1CMT} (AUC_{1CMT} minus AUC_{2CMT}, in mg·h/L; $r^2 = 0.29$, $P = 0.12$; see **Figure 1**, **Supplemental Digital Content 1**, http://links.lww.com/TDM/A363). Furthermore, based on visual inspection of the fit of the time courses of plasma concentrations residual plots and the Akaike criterion values, the fitting of the concentration–time data was similar in morbidly obese and nonmorbidly obese subjects.

DISCUSSION

Vancomycin PK in adults is best described by a 2-compartment model.[2] The pertinent question is whether approximating vancomycin PK by a 1-compartment model results in a clinically significant bias in the AUC estimates. The present findings suggest that well-constructed 1-compartment population models are acceptable as the basis for Bayesian-guided vancomycin dosing in individual patients. Although the PK of vancomycin in adults can be most accurately described using multi-compartmental models,[9,11] the difference in vancomycin drug exposure, expressed as AUC and as estimated using the 1-compartment population model, was small relative to the noncompartmental and 2-compartment approaches from a practical, clinical perspective. A slight underestimation of drug exposure was anticipated because the 1-compartment model does not characterize all the area under the α-distribution phase (Fig. 1). Although difference between AUC_{1CMT} and AUC_{2CMT} was significant ($P < 0.05$), this was considered clinically significant given that the deviation was <20%. A difference of 15 mg·h/L between AUC_{1CMT} and AUC_{2CMT} is unlikely to alter efficacy or toxicity outcomes, given that recommended AUC_{0-24} target is 400–600 mg·h/L.[2]

TABLE 3. Comparison of the AUC_{1CMT}, AUC_{2CMT}, and AUC_{NCA} Values After a Single Dose of Vancomycin (n = 30)

	Mean Difference (mg·h/L)	Mean Difference (%)	*P**
$AUC_{2CMT} - AUC_{1CMT}$	15.1	8.3	5.4×10^{14}
$AUC_{NCA} - AUC_{1CMT}$	13.0	7.2	1.3×10^{10}
$AUC_{2CMT} - AUC_{NCA}$	2.1	1.2	0.85

**P*-value refers to the mean differences.

AUC, area under the plasma concentration–time curve; AUC_{1CMT}, area under the plasma concentration–time curve calculated using a 1-compartment model; AUC_{2CMT}, area under the plasma concentration–time curve calculated using a 2-compartment model; AUC_{NCA}, area under the plasma concentration–time curve calculated by the linear ascending, log-linear descending trapezoidal approach.

Several factors influence the suitability of a population model for use in Bayesian dosage prediction. These factors include the number of subjects studied, blood sampling times, generalizability of the subjects with respect to the intended target population, and the representativeness of the covariates included in the population model.[17] Notably, the blood sampling design dictates the ability to adequately describe the PK profile. Vancomycin population models have been typically derived from data routinely collected from TDM services rather than prospective studies using optimal drug concentration sampling times. This questions the suitability of these models for use in Bayesian dosage forecasting programs.[12] Thus, to construct a satisfactory 1-compartment population PK model, a minimum of 2 concentrations in a single-dosing interval is needed for each subject. A 2-compartment model requires 4 concentrations per patient with at least one sample collected within the initial 0–1.5 hours after infusion, representing the distribution time period when concentrations decline rapidly. Obtaining 4 or more concentrations per patient, or concentrations within the initial distribution phase, is not practical in routine practice. For example, the largest published 2-compartment vancomycin PK model to date is derived from 1557 concentrations obtained from 398 patients. However, most samples (64%) were collected up to 10 hours after infusion, and the earliest sample was drawn 1.1 hours after infusion.[18] In another large 2-compartment population model (141 subjects, 254 concentrations), only 0.4% of concentrations were collected within 2 hours of the infusion.[19] Thus, most vancomycin population models are derived from near trough concentrations or concentrations collected after the initial distribution phase (>1.5 hours after infusion) and are therefore limited to 1-compartment analysis.[17,20–22] Future vancomycin population PK models derived from a smaller number of patients may be more cost-effective if the sample collection times are more informative. Despite limitations associated with blood sampling times, our findings suggest that a 1-compartment PK model derived from blood samples from a moderate number of patients (approximately 50–100) may be sufficient to describe the vancomycin AUC. Furthermore, the results of the present study suggest that the accuracy of AUC_{1CMT} values were similar in morbidly and nonmorbidly obese subjects. Although this is a preliminary finding because of the small sample size of morbidly obese patients, this may suggest that a well-constructed 1-compartment population model may be adequate for the purposes of Bayesian forecasting to describe vancomycin AUC in morbidly obese patients.

To our knowledge, this was the first study to compare differences in vancomycin AUC values estimated using a noncompartmental, 1-compartment, or 2-compartment model. Strengths of this study included the richly-sampled cohort and the assessment of single-dose PK and $AUC_{0-\infty}$ rather than AUC_{0-24}. This enabled the extrapolation of findings to steady-state conditions, which is important given that TDM is commonly performed when a patient has already received multiple doses. Although the study cohort was heterogenous and included patients with diverse medical histories and variable renal function, these patient characteristics are consistent with those observed in real-world populations prescribed vancomycin. Furthermore, the modelling approaches were able to account for interpatient variability in vancomycin PK.

The present study included a moderate sample size and a population limited to adult subjects with stable renal function. Vancomycin is often prescribed to patients with unstable renal function. Further research is required to assess whether a 1-compartment model is sufficient to predict exposure to vancomycin in special patient populations (such as those who are critically ill, have unstable renal function, or dialyzed patients) using different Bayesian dosing software.

CONCLUSIONS

This study demonstrated that a 1-compartment model may be sufficient to describe exposure (AUC) to vancomycin for the purpose of guiding drug dosage. However, further research is required to assess the appropriateness of a 1-compartment model to predict exposure to vancomycin in special patient populations. Furthermore, parameters affecting the optimal sampling time for AUC estimation using a single serum vancomycin concentration must also be assessed.

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