PHARMACOTHERAPY

ORIGINAL RESEARCH ARTICLES

Review and Validation of Bayesian Dose-Optimizing Software and Equations for Calculation of the Vancomycin Area Under the Curve in Critically Ill Patients

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Background Vancomycin area under the concentration-time curve (AUC) has been linked to efficacy and safety. An accurate method of calculating the AUC is needed.

Methods Bayesian dose-optimizing software programs available for clinician use and first-order pharmacokinetic equations were evaluated for their ability to estimate vancomycin AUC. A previously published rich pharmacokinetic data set of 19 critically ill patients was used for validation of the AUC estimation. The AUC estimated using subsets of the full data set by Bayesian software and equations was compared with the reference AUC. Accuracy (ratio of estimated AUC to the reference AUC) and bias (percentage difference of estimated AUC to reference AUC) were calculated.

Results Five Bayesian dose-optimizing software programs (Adult and Pediatric Kinetics [APK], BestDose, DoseMe, InsightRx, and Precise PK) and two first-order pharmacokinetic equations were included. Of the Bayesian programs, InsightRx was the most adaptable, visually appealing, easiest to use, and had the most company support. Utilizing only the trough, accuracy (range 0.79–1.03) and bias (range 5.1–21.2%) of the Bayesian dose-optimizing software were variable. Precise PK and BestDose had the most accurate estimates with the accuracy values of BestDose exhibiting the most variability of all the programs; however, both programs were more difficult to use. Precise PK was the least biased (median 5.1%). Using a single nontrough value produced similar results to that of the trough for most programs. The addition of a second level to the trough improved the accuracy and bias for DoseMe and InsightRx but not Precise PK and BestDose. APK did not reliably estimate the AUC with input of two levels. Using two levels, the pharmacokinetic equations produced similar or better accuracy and bias as compared with Bayesian software.

Conclusion Bayesian dose-optimizing software using one or more vancomycin levels and pharmacokinetic equations utilizing two vancomycin levels produce similar estimates of the AUC.

Key Words vancomycin, infectious disease, pharmacodynamics, pharmacokinetics.

(Pharmacotherapy 2018;38(12):1174–1183) doi: 10.1002/phar.2191

Conflict of interest: Our health system currently has access to APK and includes APK as a possible methodology of calculating vancomycin dosing on our vancomycin dosing protocol. At no point was any company given a guarantee that our health system would pursue a contract. At the writing of this manuscript, our health system has no ongoing contract with or immediate plans to pursue any contract with any of the companies mentioned. The authors have declared no conflicts of interest with any of the companies discussed in this article.

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Vancomycin is a widely used intravenous antibiotic for empirical and definitive treatment of gram-positive organisms including methicillin-resistant *Staphylococcus aureus*.[1] Current treatment guidelines recommend monitoring trough levels to minimize toxicity and maximize efficacy.[2] Data suggest that the vancomycin pharmacodynamic parameter most closely linked to efficacy is the ratio of the daily area under the curve (AUC) to minimum inhibitory concentration (MIC).[3] An AUC:MIC ratio in excess of 400 for treatment of *S. aureus* was postulated as an important metric to increase the likelihood of efficacy[1–10]; however, this specific value remains controversial.[3] Nephrotoxicity, a dose-limited adverse reaction, was associated with trough levels greater than 15 mg/L and also an AUC in excess of 700–1300 hr·mg/L.[11–13] The trough level poorly correlates to AUC, and using the trough to adjust vancomycin dosing may lead to suboptimal treatment regimens.[8, 14] An argument in favor of more robust monitoring was well described Pai and collagues who proposed two approaches.[8] The first approach includes collection of two postinfusion vancomycin levels with analysis using first-order pharmacokinetic equations. The second methodology is the Bayesian approach that combines population estimates of vancomycin pharmacokinetics (Bayesian priors) with patient-specific levels. Bayesian dose-optimizing software is required for this second methodology. Most programs performing Bayesian estimation are highly technical and require extensive training for use. Programs designed for clinical use are available but few in numbers, where the majority are used for research purposes. The purpose of this study was to provide an estimate of the accuracy and bias of commercially available Bayesian dose-optimizing software using a rich pharmacokinetic data set previously collected from critically ill patients.[14] First-order pharmacokinetic equations, as proposed by Pai and colleagues, were also evaluated.[8] In addition, review of the available software was conducted. For this article, the abbreviation AUC is used interchangeably with daily AUC or $AUC_{0–24}$.

Methods

Study Setting

A prospective observational study of vancomycin pharmacokinetics was conducted in an intensive care unit and was described previously.[14] This data set was used for validation of vancomycin AUC estimates. In brief, 19 adult patients receiving vancomycin as part of their care were enrolled. Vancomycin serum levels were taken during the vancomycin infusion, at the end of the infusion, at 60, 120, and 300 minutes following the infusion, and immediately before the next dose. Sampling occurred concurrently with the third or greater sequential dose of intravenous vancomycin. Pharmacokinetic analysis was conducted by a noncompartmental intermittent intravenous infusion model at steady state. The AUC was calculated by the linear-log trapezoidal rule.

Bayesian Dose-optimizing Software

Available programs were identified via multiple methods: search of the Internet, archives of e-mail list servers (Society of Infectious Diseases Pharmacists and the infectious diseases practice and research network of the American College of Clinical Pharmacy), personal communication with clinicians, and a search of PubMed from inception to May 2018 using the search terms "Bayesian" and "vancomycin." Programs identified via any of these methods had to meet these criteria to be evaluated: utilize the Bayesian approach, commercially available, compatible with the Microsoft Windows operating system, and a low learning curve allowing for clinician use without extensive technical training. Programs that did not appear to be currently supported by the company (updates not available or supported) were excluded. Several programs can be directly integrated into modern electronic health records; we evaluated all software in the stand-alone version of these programs that functioned outside of the electronic health record.

Estimation of AUC by Bayesian Dose-optimizing Software and Equations

For the intent of this study, the AUC calculated using the linear-log trapezoidal rule from the full data set was considered the reference AUC (AUC_{REF}). The AUC_{REF} was verified in Bayesian software that allowed for input and analysis of the full data set for each patient. Using the rich pharmacokinetic data set (19 subjects), the AUC_{REF} was compared with the AUC estimated by each Bayesian program. Comparison was made using five subsets of the full data set: trough only (AUC_T), the 5-hour postinfusion level (AUC_{5H}), trough and 1-hour postinfusion level ($AUC_{1H,T}$), trough and 2-hour

postinfusion level ($AUC_{2H,T}$), and the trough and the level taken before the trough ($AUC_{next,T}$). The level taken before the trough was collected an average of 2.8 hours before the trough level. If different models or other modifications of the estimation were available, these were tested. First-order pharmacokinetic equations, as described by Pai and colleagues as equations 4 and 5, were evaluated.[8]

Study End Points

Accuracy was defined as the median ratio of the estimated AUC to AUC_{REF} ($AUC:AUC_{REF}$). Bias was defined as the median of the absolute value of the percentage difference of the estimated AUC from AUC_{REF} [$(|AUC - AUC_{REF}|/AUC_{REF}) \times 100$]. Several end points were evaluated: accuracy and bias of each methodology for each subset of the full data set; accuracy and bias of AUC_T as compared with AUC_{5H}; accuracy and bias with two levels in Bayesian software as compared with trough only; accuracy and bias of Bayesian software compared with equations with two levels; and, finally, each Bayesian program was reviewed for ease of use, cost, functionality, and clinical utility.

Statistical Analysis

First, the estimated AUC calculated from programs and equations from each subset of the full data set was compared with the AUC_{REF} by the Wilcoxon signed rank test for nonparametric data. Coefficients of determination were calculated using simple linear regression. Second, accuracy and bias produced from AUC_T were compared between programs by the Wilcoxon signed rank test. Third, the accuracy and bias from AUC_T were compared with AUC_{5H} for each program. Fourth, accuracy and bias of AUC_T were compared with $AUC_{1H,T}$, $AUC_{2H,T}$, and $AUC_{next,T}$ for each program. Fifth, accuracy and bias from $AUC_{1H,T}$, $AUC_{2H,T}$, and $AUC_{next,T}$ produced from equations 4 and 5 were compared with that of each program. P values less than 0.05 were considered statistically significant. Analyses were performed using Stata v.14.2 (StataCorp, College Station, TX, USA). This study was approved by the institutional review board.

Results

One level in a single patient was excluded from all AUC calculations because it was determined to be erroneous. The median and mean AUC as calculated by the linear-log trapezoidal rule was 579 hr·mg/L (range 445–912 hr·mg/L) and 604 ± 109 hr·mg/L, respectively.[14] The median AUC estimated from inputting the full data set into Bayesian software ranged from 582–610 hr·mg/L (Tables 1 and 2). Seven methodologies of AUC calculation were evaluated: five Bayesian programs and equations 4 and 5[8] (Figure 1). For the Bayesian programs, pricing, models, ease of use, and other general characteristics are presented in Table 3. The following is a review of each method of AUC calculation.

Adult and Pediatric Kinetics

Adult and Pediatric Kinetics (APK) from RxKinetics (http://www.rxkinetics.com/apk.html) is a simple inexpensive program that requires minimal training to use with proficiency. Two settings (normal and outlier) are available, although the model parameters are not apparent. Doses are input as a single dosing regimen instead of as individual doses. This limits the ability to input loading doses or a complicated regimen (e.g., input of regimen allows one to specify the dose, frequency, and number of doses only [vancomycin 1000 mg every 8 hours for 7 doses]; it does not allow input of specific dosing times). Although up to three postinfusion levels can be input, the program did not reliably return results when inputting more than one level (frequently returned error message). Demographic data can be saved, but dosing regimens and serum levels are not saved. Customer and technical support is limited.

BestDose

BestDose (http://www.lapk.org/bestdose.php) is only available upon request as an installed application; however, a Web-based program to replace BestDose is currently in development. For the current version, navigation is difficult and not intuitive, requiring multiple steps to load population models, input data, and fit data. Dosage regimens (vancomycin 1000 mg every 8 hours for 7 doses) can be entered, or doses and dosing times can be added manually. BestDose allows for modifications to the population model and for additional models to be uploaded; however, technical training is required to use this functionality. All patient data are saved.

Table 1. Accuracy of the Estimated AUC: Ratio of Estimated AUC:AUC_{REF}

Program	AUC_T:AUC_{REF}	$AUC_{1H,T}$:AUC_{REF}	$AUC_{2H,T}$:AUC_{REF}	$AUC_{next,T}$:AUC_{REF}	Full data set/AUC_{REF}
APK	0.87 (0.81–0.94)	NA[a]	NA[a]	NA[a]	NA[a]
BestDose	1.01 (0.84–1.08)	1.03 (0.86–1.06)	1.02 (0.91–1.06)	1.01 (0.82–1.06)	1.01 (0.98–1.02)
DoseMe	0.79 (0.75–0.84)	0.92 (0.87–0.97)	0.87 (0.84–0.93)	0.83 (0.79–0.86)	1.04 (1.00–1.05)
InsightRx	0.84 (0.77–0.88)	0.88 (0.83–0.92)	0.87 (0.86–0.91)	0.86 (0.78–0.91)	1.01 (0.98–1.02)
Precise PK	1.03 (0.92–1.05)	1.07 (1.01–1.12)	1.04 (1.01–1.12)	1.03 (0.95–1.06)	1.05 (1.00–1.10)
Equation 4[8]	NA[b]	1.0 (0.93–1.05)	0.94 (0.88–0.97)	0.88 (0.81–0.93)	NA[b]
Equation 5[8]	NA[b]	1.09 (0.96–1.14)	0.98 (0.92–1.01)	0.89 (0.85–0.97)	NA[b]

Calculated as estimated AUC:AUC_{REF}. All data reported as median (25th–75th percentiles). A ratio less than 1.0 indicates the methodology underestimates the AUC_{REF}.

AUC = area under the curve; AUC_{REF} = reference AUC as calculated by linear-log trapezoidal rule; AUC_T = estimated AUC using vancomycin trough level only; $AUC_{1H,T}$ = estimated AUC using trough and 1-hour postinfusion levels; $AUC_{2H,T}$ = estimated AUC using trough and 2-hour postinfusion levels; $AUC_{next,T}$ = estimated AUC using trough and the level taken before the trough; NA = not available.

[a]For APK, input of more than one vancomycin level often led to errors; therefore, the assumption was made that this is not a reliable function of APK; any values reported were excluded.

[b]Equations require collection of at least two vancomycin levels and cannot produce results when using just the trough levels.

Table 2. Bias of the Estimated AUC: Percentage Difference of the Estimated AUC from the AUC_{REF}

Program	AUC_T	$AUC_{1H,T}$	$AUC_{2H,T}$	$AUC_{next,T}$	Full data set
APK	13.1 (7.4–18.9)	NA[a]	NA[a]	NA[a]	NA[a]
BestDose	11.2 (5.1–18.3)	8.1 (3.6–18.3)	8.8 (4.4–11.6)	10.6 (5.7–20.2)	8.3 (2.9–21.0)
DoseMe	21.2 (16.3–24.6)	8.4 (4.6–13.2)	13.3 (6.6–16.1)	16.8 (13.8–21.0)	5.0 (3.4–6.7)
InsightRx	16.4 (11.8–22.6)	12.2 (8.0–16.9)	12.6 (9.1–14.5)	13.9 (9.5–22.1)	2.6 (0.7–5.3)
Precise PK	5.1 (3.0–11.2)	8.9 (1.8–12.2)	4.7 (2.9–12.8)	5.2 (3.3–8.9)	5.0 (2.2–10.5)
Equation 4[8]	NA[b]	6.5 (2.0–12.2)	7.1 (3.3–11.9)	15.1 (10.8–19.1)	NA[b]
Equation 5[8]	NA[b]	11.0 (3.9–14.4)	5.5 (1.3–10.1)	11.3 (7.6–15.3)	NA[b]

Calculated as $[(|AUC - AUC_{REF}|/AUC_{REF}) \times 100]$. All data reported as median (25th–75th percentiles).

AUC = area under the curve; AUC_{REF} = reference AUC as calculated by linear-log trapezoidal rule; AUC_T = estimated AUC using the vancomycin trough level only; $AUC_{1H,T}$ = estimated AUC using the trough and 1-hour postinfusion levels; $AUC_{2H,T}$ = estimated AUC using the trough and 2-hour postinfusion levels; $AUC_{next,T}$ = estimated AUC using the trough and the level taken before the trough; NA = not available.

[a]For APK, input of more than one vancomycin level often led to errors; therefore, the assumption was made that this is not a reliable function of APK and any values reported were excluded.

[b]Equations require collection of at least two vancomycin levels and cannot produce results when using just the trough levels.

DoseMe

DoseMe (https://doseme-rx.com/) is a Web-based program requiring minimal training because navigation is intuitive; however, multiple screens are required for data input and viewing results. DoseMe provides an option to adjust the trust in serum assay results: normal, high, or skeptical. Doses may be entered individually or as a dosage regimen. Serum vancomycin levels greater than 50 mg/L are not allowed. DoseMe is visually rich and provides graphic depictions of patient and population data. All patient data are saved. Customer and technical support is responsive.

InsightRx

InsightRx (https://insight-rx.com/) is a Web-based program that requires minimal training, is intuitive, and all data are input and available from a single screen. InsightRx is the most adaptable of the programs with four available pharmacokinetic models and multiple analytical options for each patient: maximum a posteriori probability Bayesian, flattening priors, least squares regression, and others. Doses must be input individually without the ability to input a fixed regimen. InsightRx is visually rich and displays multiple useful graphs. Probability of achieving target goals (AUC higher than 400) and probability of toxicity are directly displayed for different regimens. All patient data are saved. Customer and technical support is the most responsive of all tested with active technical monitoring (an e-mail was received the same day that the input generated an error message). Models are occasionally updated by incorporating vancomycin regimens and serum levels entered by end users to improve model fit. The developers actively seek out research opportunities with clinicians to better describe covariates and improve models. Overall, InsightRx was the easiest to use, the most visually appealing, best technical and customer support, and most likely

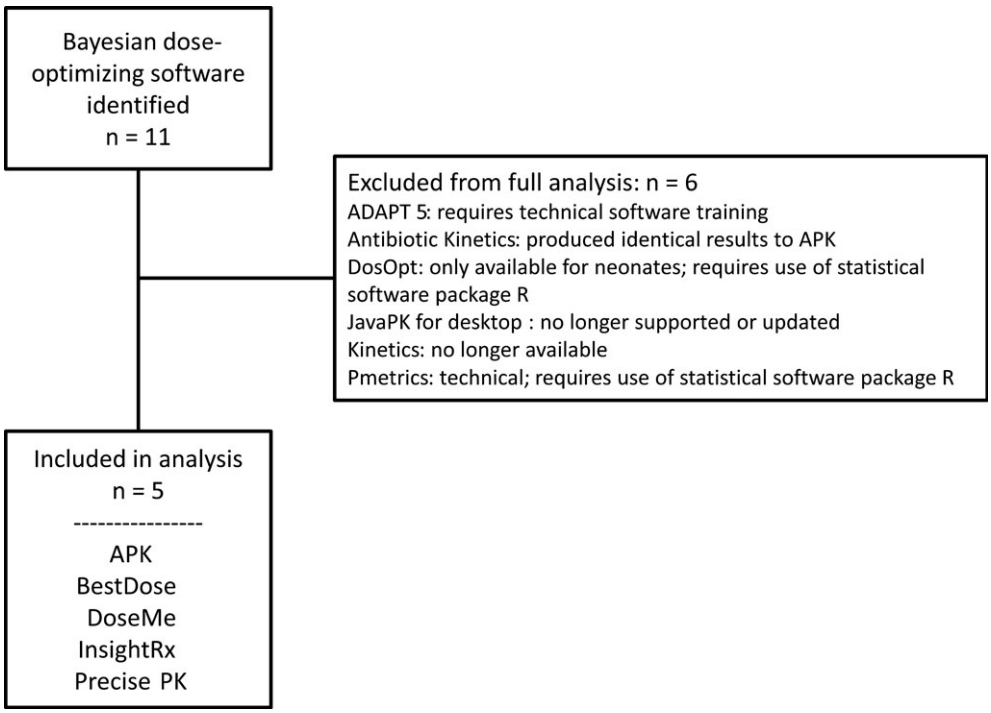

Figure 1. Flowchart of included and excluded Bayesian dose-optimizing software.

to be continually improved to maximize customer experience and improve pharmacokinetic estimation.

Precise PK

Precise PK (https://precisepk.com/) is a downloadable program that requires moderate training. The user must navigate through multiple screens to input the required information to obtain results. Identifying the correct method of inputting data and the desired output was not intuitive. Doses and serum levels can be input individually or as a fixed regimen. Graphs of patient data are displayed. All patient data are saved. Customer and technical support is limited.

Equations 4 and 5

These equations are described Pai and colleagues, and we refer the reader to their article for a full detailed explanation.[8] A simple formula can be built into a spreadsheet program such as Microsoft Excel. After these formulas are constructed in a spreadsheet program, the only inputs required are two vancomycin-level values, their associated times of collection, and the time of vancomycin infusion. Equation 4 is predicted to underestimate the true AUC and equation 5 to overestimate the true AUC.[8]

Bayesian dose-Optimizing Software with Trough Only

In APK, changing the setting from "normal" to "outlier" had no significant effect on AUC_T ($p=0.24$). In DoseMe, changing the trust in assay results from "normal" to "high" had no significant effect on AUC_T ($p=0.90$). In InsightRx, the Thomson[16] and Goti[17] models were similar ($p=0.73$) and fit the AUC_{REF} better than the Buelga model[15] ($p<0.001$ for both comparisons). Because the two models[16, 17] did not differ significantly and the Thomson model is considered the default, only data from that model are shown.

Accuracy is displayed in Figure 2 for methodologies using the trough value only. AUC_T estimated by BestDose and Precise PK were both nonsignificantly different from the AUC_{REF} ($p=0.55$ and $p=0.66$, respectively). As can be seen in Figure 2, although highly accurate, BestDose did have the widest distribution of estimates. The program that provided the least biased estimation of AUC_{REF} was Precise PK. AUC_T estimated by the other programs underestimated and were significantly different from AUC_{REF} ($p<0.05$). In APK, AUC_{5H} produced substantially less accurate and more biased estimates than AUC_T ($p<0.05$). For all other programs, AUC_T and AUC_{5H} produced similar estimates ($p>0.05$ for all comparisons).

Table 3. Comparison of Bayesian Dose-optimizing Software

	Availability	Pricing	EHR integration	Required training	Goodness-of-fit information	Bayesian model
APK (http://www.rxkinetics.com/apk.html)	Downloaded and installed	One user: $150 Site: $390 Personal use: $75	No	Minimal	Yes; displays warning if poorly fit	Multiple pharmacokinetic references with no single model identified
BestDose (http://www.lapk.org/bestdose.php)	Downloaded and installed	Free	No	Extensive	Yes; but no warning if poorly fit	Multiple pharmacokinetic references with no single model identified
DoseMe (https://doseme-rx.com/)	Web based	Not publicly available; higher cost than comparators	Yes, available for EPIC App Orchard, Cerner Millennium, and Allscripts	Minimal	No fit information; no warning if poorly fit	Reference[15]
InsightRx (https://insight-rx.com/)	Web based	Not publicly available; higher cost than comparators	Yes, available for EPIC App Orchard; developing integration for Cerner Millennium and Meditech, and Centricity	Minimal	Yes; displays warning if poorly fit	Reference[16] [default] Reference[15] Reference[17] Reference[18] [for pediatrics]
Precise PK (https://precisepk.com/)	Downloaded and installed	Annual per institution: $599 for three devices $799 for 20 devices $1199 for 100 devices	No	Moderate	No fit information; no warning if poorly fit	Multiple pharmacokinetic references with no single model identified

APK = Adult and Pediatric Kinetics; EHR = electronic health record.

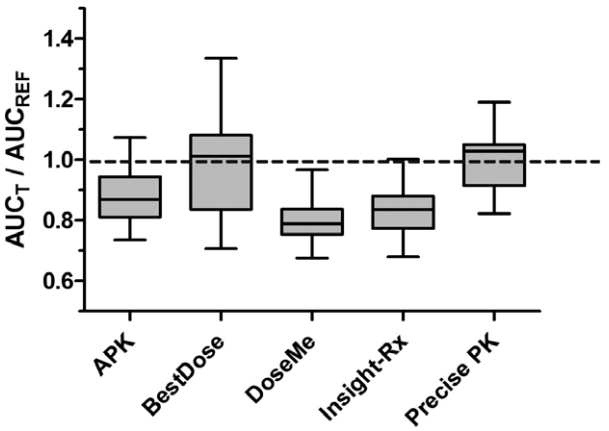

Figure 2. Box plot of the ratio of AUC_T:AUC_{REF} for Bayesian dose-optimizing software. AUC = area under the curve; AUC_T = estimated AUC when using only the trough value; AUC_{REF} = AUC calculated by the linear-log trapezoidal rule using the full data set.

Bayesian Dose-optimizing Software and Equations with Two Postinfusion Levels

Because APK failed to produce results for many of the patients using more than one vancomycin level per patient, it was excluded from this part of the analysis. Several estimates were similar to AUC_{REF}: all calculations using BestDose, $AUC_{next,T}$ estimated by Precise PK, $AUC_{2H,T}$ using equation 5, and $AUC_{1H,T}$ using equation 4 (Table 1). All other estimations differed significantly from AUC_{REF} ($p<0.05$). Although differences existed among the different methodologies, the best level to use in addition to the trough was either the 1-hour or 2-hour postinfusion levels (Tables 1 and 2).

The addition of a vancomycin level to the trough level did not reduce bias for Precise PK or BestDose ($p>0.05$), but it did reduce the bias for DoseMe and InsightRx ($p<0.05$; Table 2).

For equations 4 and 5, $AUC_{1H,T}$ as compared with $AUC_{2H,T}$ produced similar estimations ($p>0.05$; Table 2). $AUC_{next,T}$ was more biased than $AUC_{1H,T}$ or $AUC_{2H,T}$ (Table 2). $AUC_{1H,T}$, $AUC_{2H,T}$, and $AUC_{next,T}$ all produced similar or more bias using Bayesian software as compared with that of $AUC_{1H,T}$ and $AUC_{2H,T}$ from equations 4 and 5 ($p<0.05$ in favor of equations 4 and 5 or p was not significant for all comparisons).

Discussion

Because AUC may be a more predictive value for success and safety than a trough level,[3–10, 12, 13, 19–23] an accurate methodology for determining AUC is needed. Multiple methods of calculating the AUC are currently available for clinician use. The Bayesian programs that were evaluated vary substantially in cost, functionality, and level of company support.

When utilizing trough-only values, accuracy and bias of Bayesian software ranged from 0.79–1.03 and 5.1–21.2%, respectively. The most accurate and least biased program was Precise PK; however, this program was one of the more difficult to navigate and use and is only available as a downloadable program. If a single level is used with Bayesian software, it was noted that using the trough or another level during the beta-elimination phase produces similar estimates; this is consistent with findings from others[24] and allows for nontrough values to be used with reasonable assurance of similar accuracy and bias.

Using the trough and an additional level improved the accuracy and bias of DoseMe and InsightRx as compared with the trough only. For programs and the equations, the best level to use in addition to the trough was one drawn 1–2 hours after the end of the infusion; however, a nonpeak level ($AUC_{next,T}$) produced reasonable estimates. When collecting two postinfusion levels, Bayesian software produced similar estimates as compared with equations 4 and 5.

Variation in AUC estimates by Bayesian programs may be due to differences in the pharmacokinetic model or the inclusion of true peak levels in the Bayesian prior. These models nonspecifically included intensive care unit patients similar to those included in the study used for model validation.[15–17, 25] However, including intensive care patients in the Bayesian prior (by utilizing the model based on Goti and colleagues[17]) did not produce better estimates than using a methodology that excluded these patients (such as the model based on Buelga and colleagues[15]). For those programs that underestimated the AUC, visual examination of estimated time-concentration curves identified apparent underestimation of the peak. Interestingly, the model utilized by DoseMe (based on Buelga and colleagues)[15] only included peaks collected 3 hours after the end of the infusion. Several models used by InsightRx[16, 17] did not appear to include many peak levels. Because the standard practice for many years has been to collect trough levels only, many of the published contemporary models may not accurately estimate

peak concentrations and consequently may not accurately estimate AUC.

With the exception of Precise PK and BestDose, each program underestimated AUC_{REF}. We considered the possibility that the AUC_{REF}, as calculated by the linear-log trapezoidal rule, was inaccurate. However, we believe AUC_{REF} to be a fairly close approximation of the true AUC for several reasons: input of the full data set into Bayesian software provided very close estimates of the AUC_{REF} (Tables 1 and 2); equations 4 and 5 resulted in accuracy and bias very similar to that described elsewhere (equation 4 and 5 had ratios [estimated AUC:AUC_{REF}] of 0.99 and 1.02, respectively[8]); and AUC_{REF} was similar to what was published previously.[25]

Although variation in estimates is present, Bayesian programs are a substantial improvement compared with trough-only monitoring (without the Bayesian approach). The correlation of trough to AUC has been reported to be less than 50% ($r^2 < 0.50$).[8, 14] In contrast, the Bayesian software evaluated had a correlation (AUC_T to AUC_{REF}) of 70–85% (r^2 of 0.70–0.85; data not shown) when using the trough only; these values are similar to other published literature with trough-only Bayesian estimation.[26] Although some methodologies produced more accurate estimates, all methodologies produced average accuracy ratios of 0.80 or higher and bias of less than 20% (with the exception of DoseMe with AUC_T). This degree of accuracy is likely adequate when targeting an AUC of 400–600 hr·mg/L. However, methodologies that are less accurate or more biased may result in clinicians making unnecessary changes to the vancomycin dosing regimen.

Bayesian software offers several advantages to first-order pharmacokinetic equations; these are described elsewhere.[8] Briefly, use of equations is a static estimation of AUC during the specific time period when levels are collected. This approach lacks the flexibility of dynamic modeling that can predict future performance and integrate additional clinical information to determine the impact of dose modification. Bayesian software has the ability to estimate the time to steady state and the AUC upon reaching steady state. Bayesian software can also estimate the AUC when levels are not collected at the intended times.

Another benefit of Bayesian software is estimation using Bayesian priors (data from previous patients on which the model is based). In this study, several levels were possibly erroneous including one level with a reported value of 70 mg/L when the anticipated value (based on other samples) was 25 mg/L. If an erroneous level is used in pharmacokinetic equations (equation 4 or 5), it will produce an erroneous estimate of the AUC; in this case, use of the reported value of 70 mg/L with the pharmacokinetic equations led to a greater than 3.5-fold higher estimated AUC than the reference AUC. In contrast, erroneous levels will affect the output of Bayesian software to a much lesser degree due to reliance on the Bayesian prior (in this same case, overestimation of AUC by 65% in one program). In addition, several Bayesian programs will alert the clinician to values that fit poorly with the Bayesian prior and are more likely to be erroneous (Table 3).

Clinical data examining the impact of AUC-guided dosing are limited and not the focus of this article. One study included 1280 patients (734 underwent AUC-guided dosing with collection of two levels and utilization of equation 4) and found that AUC-guided dosing resulted in lower daily vancomycin doses and reduced risk of nephrotoxicity.[27] In agreement with other data,[14, 19] a large percentage of patients had adequate AUC with troughs lower than 15 mg/L. Another study evaluated BestDose with collection of a single vancomycin level.[24] AUC-guided dosing resulted in shorter durations of therapy, less nephrotoxicity, and lower troughs while maintaining similar efficacy.

Substantial limitations are present in this study that require careful consideration. First, this study was conducted in critically ill patients in a level 1 trauma intensive care unit (although not all were trauma cases) and may not be applicable in other settings. However, the similarities found in accuracy and bias in this study with use of equations 4 and 5 compared with that of Pai and colleagues[8] may mitigate this limitation. Second, the patient sample size for this study was small (19 subjects). Third, the performance of the software was examined during a single dosing interval and did not examine the predictability of Bayesian programs (one of the strengths of the Bayesian approach). Finally, calculation of AUC during continuous infusion as a methodology was not considered in this study. AUC-guided dosing can be achieved with use of continuous infusion, random vancomycin-level collection, and a simple calculation (daily AUC = concentration at steady state × 24 hrs).[28, 29] Although easy to calculate, challenges with continuous infusion may limit its widespread use.

Conclusions

Several methods of calculating AUC are now available to clinicians and allow for AUC estimation with collection of a single or multiple vancomycin levels. Using just the trough for calculation, Precise PK and BestDose were the most accurate; accuracy ratios for BestDose were the most variable of all programs. In addition, both programs were more difficult to use than others. Precise PK was the least biased. InsightRx was the most adaptable, visually appealing, easiest to use, and had the most company support. Compared with Bayesian programs, the pharmacokinetic equations produced similar or better accuracy and bias. AUC estimation with the pharmacokinetic equations can be easily implemented by constructing a spreadsheet formula but requires two vancomycin levels to be drawn and is a static estimation of AUC. The use of Bayesian software requires the purchase of software and additional training but has multiple advantages. We encourage health systems to consider carefully the benefits, limitations, and challenges of different methodologies of AUC estimation before implementation.

Acknowledgment

We would like to acknowledge the nursing staff in the neuro-trauma intensive care unit of the Legacy Emanuel Medical Center for their invaluable assistance in collecting vancomycin blood levels. This work was supported by a faculty development grant from the School of Pharmacy, Pacific University, Hillsboro, Oregon, USA.

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