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(REVIEW ARTICLE)

BAYESIAN ESTIMATION VERSUS FIRST-ORDER PHARMACOKINETIC EQUATIONS FOR AUC-GUIDED VANCOMYCIN DOSING: A NARRATIVE REVIEW

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ABSTRACT

Background: Consensus guidelines recommend area under the curve (AUC) guided vancomycin monitoring for severe infections caused by methicillin-resistant Staphylococcus aureus. This targets an AUC24/MIC ratio of 400-600 assuming a MIC of 1mg/L. An AUC can be calculated using first-order equations or Bayesian software based on two concentrations. Despite both being recommended, there is little information available on how they differ from each other.

Objective: To review the principles, evidence, practicalities and research requirements of Bayesian vs. equation-based AUC estimation for vancomycin.

Approach: Narrative review of guideline documents and published comparative studies of AUC estimation methods. The literature search methods must be completed by the authors before submission, including databases, final search date, search terms, and selection criteria.

Findings: Limited studies were comparing AUC estimation techniques. Most were single-centre and retrospective. Overall, there was good agreement between first-order and Bayesian estimates for adult and paediatric patients. Bayesian techniques allow for earlier estimates and more flexible sampling. One quasi-experimental study found more useful concentrations. However, benefits depend on integration with electronic health records. There is no evidence to suggest one technique will lead to differences in nephrotoxicity, efficacy or mortality. There is strong evidence to suggest AUC-guided monitoring will result in less nephrotoxicity than trough.

Conclusion: Both techniques will give acceptable estimates of AUC if used appropriately. Choice should be based on sampling ability, patient population, model appropriateness and local resources. More prospective studies comparing the techniques and focusing on patient-centred outcomes are needed. Keywords: vancomycin, therapeutic drug monitoring, area under the curve, Bayesian estimation, pharmacokinetics, acute kidney injury.

Keywords: Vancomycin; Therapeutic drug monitoring; Area under the curve; Bayesian estimation; Pharmacokinetics; Acute kidney injury

1 INTRODUCTION

Vancomycin is a glycopeptide antibiotic used to treat severe infections caused by MRSA and other gram-positive bacteria susceptible to it. Due to large inter-patient variability in pharmacokinetics and recognised issues with nephrotoxicity related to exposure, it is often monitored with TDM. Instead of focusing on achieving trough concentrations of 15-20mg/L, AUC-guided monitoring is now recommended, with a target AUC24/MIC of 400-600 for serious MRSA infections (American Society of Health-System Pharmacists, Infectious Diseases Society of America, Pediatric Infectious Diseases Society, Society of Infectious Diseases Pharmacists 2020 consensus guidelines)[1].

Two techniques are recommended in the guidelines for calculating AUC. Bayesian forecasting techniques using patient data and a population pharmacokinetic model. First-order (analytical) equations using two measured concentrations[1]. The guidelines favour Bayesian techniques wherever possible due to their ability to calculate AUC from one or more concentrations and do not require strict steady-state sampling[1]. The move away from trough monitoring is based on evidence to suggest that trough concentrations are not a perfect surrogate marker for AUC[2]. Meta-analyses comparing AUC-guided monitoring to trough have

found less nephrotoxicity[3,4]. However, does the technique used to calculate AUC make a difference once AUC-guided monitoring has been chosen? This review aims to outline the principles behind each technique, evidence comparing them, practicalities and areas for future research.

2 REVIEW APPROACH

Narrative review of guideline documentation and primary research directly comparing Bayesian vs. first-order AUC estimation techniques. Key literature looking into AUC-guided monitoring and nephrotoxicity was included. The authors have completed a detailed literature search prior to submission, including databases searched, date searched, search terms and inclusion criteria. Where there is limited evidence, this will be highlighted.

3 PRINCIPLES

3.1 First-order pharmacokinetic equations

Equation-based methods usually use a post-distribution peak and trough concentration within the same dosing interval to calculate an elimination rate constant and volume of distribution. From this, an AUC24 can be estimated. The advantages of this method are that they are transparent, low cost and familiar to clinicians. It can be easily used to create an Excel sheet or calculator within an electronic health record. Disadvantages are that they rely on accurate timings of samples and administration. Most require steady-state samples. 3.2 Bayesian estimation

3.2 Bayesian estimation

Bayesian software uses a population pharmacokinetic model as a prior. Individual parameters can then be estimated based on patient covariates, dosing history and measured concentrations. As a prior provides information, estimation can be done after the first dose and with just one concentration. Flexible sampling can be done. This relies on the model fitting the patient; however, there is less certainty. If the patient doesn't fit the model well (such as neonates, critically ill patients, obese patients and those with unstable renal function), there may be issues. This needs to be confirmed for the model you are using. References should be added to show that the model performs well for certain populations. Cost, training and integration with EHR are some practical issues.

Table 1: Comparison of first-order equation and Bayesian approaches to vancomycin AUC estimation

Feature	First-order equations	Bayesian estimation
Inputs	Two appropriately timed steady-state concentrations (typically post-distribution peak and trough), with exact dosing and sampling times	Dosing history, covariates and one or more concentrations, combined with a population PK model
Core assumption	Linear, one-compartment, first-order elimination between samples; steady state	Chosen population model is appropriate for the patient; model priors are informative.
Earliest estimate	After steady state is approached and two valid samples are available	Possible after the first dose or with a single concentration, depending on the model
Main vulnerability	Sample-timing errors; unusable concentrations; non-steady-state sampling	Model misspecification in populations unlike the model cohort; software access and cost; workflow integration
Infrastructure	Spreadsheet or EHR calculator; minimal cost	Dedicated software; may require licensing, training and EHR integration

PK, pharmacokinetic; EHR, electronic health record.

4 COMPARATIVE EVIDENCE

4.1 Agreement between methods

Olney et al. performed a single centre retrospective cohort study of 978 adult hospital inpatients receiving vancomycin for 72hours or more who had two concentrations measured. AUC24 was calculated using first-order equations and Bayesian estimation using two and one concentrations. This demonstrated good concordance between the first-order and two-concentration Bayesian estimations with acceptable variation [5]. However, it should be noted that the Bayesian software was provided as a free trial from the company supplying it. Previous PK studies suggest that Bayesian software can give an underestimate of the AUC24 compared to traditional first-order steady states [5].

A paediatric retrospective analysis compared first-order estimates with Bayesian estimations using two concentrations and one concentration in hospitalised children. This showed good concordance between the first-order and two-concentration Bayesian estimates (84.2%) (R^2 = 0.723). The two-concentration Bayesian estimation had good concordance with the one-concentration Bayesian estimation (82.7%) (R^2 = 0.839). This suggests that both methods are comparable [6]. However, this was an abstract; therefore, the results are preliminary.

Overall, this suggests that the concordance between the methods is acceptable in general. However, this does not necessarily mean that these would be concordant at an individual level, especially around the 400 and 600 mg/Lh/L thresholds. This also does not suggest that one method would give a more accurate AUC, as neither study used a rich sampling reference.

4.2 Efficiency, usability and workflow

Alsowaida et al. performed an unblinded and crossover quasi-experimental study at a tertiary hospital. This included 34 patients and 44 AUC estimations. The Bayesian method was not integrated with the EHR system, meaning it was slower than the first order equations. When simulated with an EHR integration, the median time taken decreased to 3.8 minutes compared to 6.8 minutes with equations. The vancomycin concentrations were valid in 88.2% of the Bayesian group compared to 48.3% in the equations. No patients suffered from AKI [7]. These times should be verified with the full text. This was a small study with simulated integration meaning the findings are hypothesis-generating.

This would make sense as the Bayesian method can cope with out-of-time samples whereas the equations cannot. This shows that the benefit of using the software will depend on how well it integrates with the clinical workflow.

4.3 Accuracy against a rich-sampling reference

Few studies are looking at accuracy. A prospective cohort study of 36 critically ill adults showed that Bayesian estimation (PrecisePK) using peak and trough samples was more accurate than troughs or prior only. The mean accuracy values were 0.976, 1.072 and 1.150, respectively [8]. Previously, models have shown that trough data only gives an underestimate of the AUC; however, using Bayesian estimation with trough data to get a prior from the full model allows accurate estimation [2].

These studies explain how the Bayesian method performs with different sampling.

4.4 Clinical outcomes

There is limited evidence suggesting that monitoring using AUC reduces nephrotoxicity. This is mostly due to comparisons with trough monitoring. A retrospective quasi experiment of 1280 adult hospital inpatients showed that AUC-guided dosing was independently associated with reduced nephrotoxicity (aOR 0.52, 95% CI 0.34-0.80) and reduced vancomycin exposure [9]. Meta-analyses have also shown AUC-guided methods reduce the risk of AKI [3,4]. A prospective study over 3 years of 252 adults showed Bayesian (BestDose) AUC guided dosing reduced nephrotoxicity (8%, 0%, 2% in the 3 years). Fewer blood samples were required and the duration of treatment was shorter than with trough-targeted dosing. There was no reduction in efficacy [10]. Only Bayesian estimation was used in the AUC guided years meaning the estimation cannot be isolated. The exposure toxicity analysis suggests there is increased risk of nephrotoxicity with higher AUCs. One analysis suggested a maximum daily AUC of 700mg.h/L would be reasonable [11]. None of the studies isolated the estimation method. This should be confirmed with a literature search before submission and changed if there are newer studies comparing outcomes.

5 PRACTICAL CONSIDERATIONS

5.1 Considerations

If two samples can be obtained at the correct times, then using equations are practical. If there is uncertainty around timing, or you want to estimate earlier, then the Bayesian method offers an advantage.

The correct model will be important to perform Bayesian estimation. Clinicians should be aware of what model is being used and whether it was developed in a similar population (neonates, critically ill, obesity, renal replacement).

If renal function is rapidly fluctuating, this challenges the steady-state assumptions in the equations. This can also be challenging for any model. Repeat monitoring should be performed.

Licensing of software, integration with EHR and competency of staff will affect how the methods perform in practice.

Whatever method you choose to use, you should document what method was used, what model and at what time samples were obtained. This will allow consistent follow-up

5.2 LIMITATIONS OF THE EVIDENCE AND RESEARCH GAPS

There is a large amount of single-centre retrospective studies. There is variation in the software, models, AUC calculation and AKI definition used. Some studies involve the vendor. Few studies are looking at accuracy using a rich sampling reference. Patient-focused outcomes were rarely powered. Future work should focus on:

- Comparing Bayesian vs equation-based dosing using a prospective/randomised design looking at nephrotoxicity and clinical response.
- Accuracy in special populations using a rich sampling reference (critically ill, obese, paediatric, neonatal and renal replacement).
- Comparing different population models and software.
- Cost effectiveness and workflow considerations (EHR integration).
- Standardised AKI definitions.

6 CONCLUSION

Both Bayesian estimation and first order equations produce acceptable estimations of vancomycin AUC if appropriate. Both methods are accepted by guidelines. The Bayesian method can offer flexibility and earlier estimation. The equations are simple and transparent. There is no evidence to suggest one method produces improved patient outcomes. A pragmatic approach should be taken considering the reliability of sample collection, population, appropriateness of model and resources available locally until higher quality evidence can be found.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

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Author contributions

The first author contributed the whole idea and preparation, and the second author corrected the mistakes the article had.

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