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COMMENTARY

Software to predict the right dose for vancomycin in a clinical environment—A commentary on: Personalised dosing of vancomycin: A prospective and retrospective comparative quasi-experimental study by Luqman Vali et al.

Jacob A. Dijkstra[1] | Agnes I. Veldkamp[1] | Elske Sieswerda[2] | Michiel van Agtmael[3]

[1]Department of Pharmacy and Clinical Pharmacology, Amsterdam University Medical Center, Amsterdam, The Netherlands

[2]Department of Medical Microbiology and Infection Control, Amsterdam University Medical Center, Amsterdam, The Netherlands

[3]Department of Internal Medicine, Amsterdam University Medical Center, Amsterdam, The Netherlands

Correspondence
Jacob A. Dijkstra, Department of Pharmacy and Clinical Pharmacology, Amsterdam University Medical Center, VU Medical Center, De Boelelaan 1117, 1081HV, Amsterdam, The Netherlands.
Email: j.dijkstra2@amsterdamumc.nl

Vancomycin is frequently used to treat Staphylococcal infections resistant to beta-lactam antibiotics. Overexposure to vancomycin increases risk of nephrotoxicity while underexposure can lead to therapeutic failure. This narrow therapeutic index makes it necessary to measure vancomycin serum concentrations aiming for an effective and justifiable dose. Often pharmacokinetic principles are used to calculate parameters that can be used to predict the vancomycin dosage that will achieve target exposure.

In this journal, Vali et al. compared the prospective results of vancomycin dose calculation using a software package (DoseMeRx) utilizing Bayesian statistic principles with retrospective results of vancomycin-dosing with a standard algorithmic approach. Bedside Bayesian-guided dosing resulted in significantly more area under the curves (AUC) measured within the acceptable range (350–450 mg/L*h) and in a significantly higher percentage of time in the acceptable range in comparison with the standard algorithmic approach.

Unfortunately, the authors were not able to relate their findings to clinical outcomes such as clinical cure or mortality, possibly due to insufficient power. Still, PK/PD modelling is the cornerstone in calculating vancomycin dosages and user-friendly bedside software can increase the availability and integration of these models in clinical practice. However, the precision of the dose calculations based on pharmacokinetic and pharmacodynamic modelling can be misleading and should not be used to determine the optimal dose without further considerations.

Several factors impact the interpretation of individual dose calculations of antibiotics based on PK/PD modelling: the target exposure (in terms of AUC/MIC) of the antibiotic that is used to predict the efficacy; clinical and pharmacological factors that influence PK and the accuracy of minimal inhibitory concentration (MIC) of the causative pathogen. We will discuss these three factors and elaborate on their influence on dose calculations.

Several studies aimed to establish a correlation between vancomycin AUC or trough concentrations and efficacy. Generally accepted vancomycin PK/PD targets are an AUC/MIC > 400 or a trough serum or plasma level (C_{trough})/MIC > 10–15.[1] Using the AUC/MIC as predicting parameter requires the use of specialized software to calculate the AUC on intermittent dosing regimens, but is generally accepted as the most appropriate PK/PD-index of vancomycin. A recent meta-analysis of several cohort studies showed that AUC/MIC guided dosing resulted in a lower incidence acute kidney injury (AKI) in comparison to trough level dosing with an odds ratio of 0.68 (95% CI: 0.46–0.99).[2] However, included studies were small, mostly retrospective, and the effect of PK/PD-based dosing on AKI and other clinical outcomes therefore need to be confirmed in larger studies.

Tissue penetration is another major determinant in choosing the right target to achieve sufficient concentrations at the target site of

the infection.[3] The extent of tissue penetration depends on the solubility of the compound in fat (or octanol - the *log P*), the acid dissociation constant (pKa), the extent of protein binding, the molecular mass and the affinity to certain transmembrane transporters, such as P-glycoprotein.[3] It could be questionable if serum or plasma concentrations are a representative factor in the treatment outcome when the tissue penetration of an antibiotic is low, while the infection is mainly situated in tissue. A good example is the high molecular mass of vancomycin and therefore low penetration characteristics. Unfortunately, despite several efforts to quantify antibiotic exposure at the target site, it has been shown that the concentration shows high variability which could not be explained by patient characteristics.[4–6] We think, however, that the predefined target should take the tissue penetration into account by applying knowledge of tissue penetration, the toxicity profile of the drug, and common sense.

Beside the optimal PK/PD target and extent of tissue penetration, the way of dosing is also of importance. Continuous vancomycin administration is increasing in clinical practice, making sampling easy as the concentration measured does not depend on the exact time of sampling, when at steady state. In a meta-analysis, the incidence of nephrotoxicity was found lower in patients treated with continuous vancomycin versus patients treated with intermittent vancomycin, with no difference in treatment failure or mortality.[7] A limiting practical factor in applying continuous vancomycin is the availability of one dedicated intravenous (IV) catheter or lumen, since vancomycin is incompatible with many other medicines and IV fluids. In the paper by Vali et al., we missed vancomycin continuous infusion simulations to collect evidence for the upcoming method of administration.

A final major determinant in defining the optimal target for an individual patient is the MIC. The MIC is defined as the lowest concentration that inhibits growth of the isolated micro-organism. The golden standard for MIC testing is broth microdilution. However, many clinical microbiological laboratories use automated systems or antimicrobial gradient strips for their first-line antimicrobial susceptibility testing (AST). These methods are rarely precise enough to be used to calculate the AUC/MIC or C_{trough}/MIC. Therefore, Mouton et al. suggested to include the epidemiological cut-off value (ECOFF) when interpreting MIC results for target attainment calculations.[8] The ECOFF is determined as the highest MIC of the bacterial species of interest without acquired resistance, that is, the wildtype population. In contrast, using the ECOFF instead of the MIC, could add potential risks of overdosing of an antibiotic for the wildtype population of a micro-organism with broad MIC ranges. For example, the suggested ECOFF of *S. aureus* for vancomycin is 2 mg/L, which would indicate that the target AUC_{0-24h} should be above 800 mg/L*h (AUC/MIC > 400). Such high AUCs increase the risk of nephrotoxicity and should not be applied in regular care. PK/PD-based modelling with accurate MIC testing therefore seems of importance to decrease risk of overdosing.

Vancomycin dosing is a complex and multifactorial challenge, where physician, microbiologist, and clinical pharmacologist should all be involved to weigh the risks of prescribing vancomycin, determine the dose, and evaluate the effect. Based on available literature, it seems that the dosing regimen should strive to achieve an AUC of 400 mg/L*h, since micro-organisms with MICs >1 mg/L result in toxic dosing regimens. However, in all cases, the multidisciplinary team should consider the low penetration of vancomycin in tissues; a frequent and critical evaluation of the effect of vancomycin on the course of the disease must be the cornerstone of effective vancomycin treatment.

COMPETING INTERESTS

There are no competing interests to declare.

ORCID

Michiel van Agtmael https://orcid.org/0000-0002-7966-6934

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