Timing of the first vancomycin maintenance dose in an acute adult hospital setting – room for improvement?

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Abstract

Title
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Introduction
Intravenous vancomycin therapy typically starts with a loading dose followed by a maintenance dose 12 to 24 hours later. In the acute hospital setting, this often results in doses being administered in the middle of the night, which is impractical for both patients and staff. This audit examined current practice and developed new guidelines to support greater flexibility in the timing of the first maintenance dose.

Methods
Data recording forms used by pharmacists to support the therapeutic drug monitoring of vancomycin were collected from two hospital sites over six weeks. Forms containing at least two vancomycin concentrations were selected and the time of administration of the first maintenance dose was recorded. Individual vancomycin pharmacokinetic parameter estimates were obtained using MAP Bayesian analysis then used to predict vancomycin concentrations 6, 8, 10, 12 and 14 hours after a banded loading dose and 20 mg/kg (capped at 3000 mg). Predicted concentrations were compared with a target range of 10 – 20 mg/L.

Results
Data were obtained from 49 patients with a mean (SD) age of 63.1 (16.7) years and weight 80.1 (27.6) kg. In all patients, creatinine clearance estimates were >40 mL/min and, according to current practice guidelines, all patients required 12 hourly maintenance dosing. The time recorded for the administration of the first maintenance dose was between 11 pm and 7 am in 30 (61%) of these patients. In 14 patients (29%), the first maintenance dose was administered >12 hours after loading. The target range was achieved with banded doses (20 mg/kg) in 65% (71%) of concentrations at 6 hours, 74% (84%) at 8 hours, 57% (67%) at 10 hours, 53% (55%) at 12 hours and 39% (43%) at 14 hours.

Conclusion
This audit has shown that current practice results in a high proportion of vancomycin maintenance doses being administered at impractical times. Allowing a more flexible time window of 6-12 hours after the loading dose for administration of the first vancomycin maintenance dose could help to alleviate this problem and reduce the risk of early subtherapeutic vancomycin trough concentrations.

Keywords: glycopeptides, therapeutic drug monitoring, dosage guidelines.

Introduction

Vancomycin is a glycopeptide antibiotic that is used in the treatment of serious infections, including methicillin-resistant *Staphylococcus aureus* (MRSA). Although studies have found that clinical and bacterial response to vancomycin is best related to the daily area under the curve to MIC ratio (AUC/MIC),[1] current practice is to monitor trough concentrations for efficacy and toxicity. The target range recommended by the Scottish Antimicrobial Prescribing Group (SAPG) is 10 – 20 mg/L, which is increased to 15 – 20 mg/L for patients with severe or deep-seated infections.[2]

Current SAPG vancomycin dosage guidelines recommend a banded loading dose based on weight (around 15 – 25 mg/kg) followed by a maintenance dose based on renal function.[2] As the guidelines state that the timing of the first maintenance dose should reflect the maintenance dosage interval, the majority of patients receive their first maintenance dose 12 or 24 hours after the start of their loading dose. Observational data and feedback comments from staff suggested that these guidelines, particularly for 12 hourly regimens, often led to dosage regimens that required vancomycin infusions to be set up overnight. This was challenging for staff and disturbing for patients. Furthermore, anecdotal observations from pharmacy and medical staff suggested that the first measured trough concentrations of vancomycin were often below the target range of 10 to 20 mg/L.

This study aimed to identify whether following current vancomycin guidelines resulted in a high proportion of maintenance doses being initiated at impractical times, to quantify the risk of low trough concentrations and to determine whether current guidance on the timing of the first maintenance dose could be modified to increase flexibility and the achievement of target trough concentrations.

Methods

Patients and data collection

A standardised data collection form was devised, piloted using data from five patients then finalised. Data were collected prospectively and retrospectively from medical and surgical wards across two hospital sites over a period of six weeks. Patients were selected for inclusion if their data were recorded on the local vancomycin prescribing and administration chart and at least two vancomycin concentration measurements were available. The following data were collected for each patient: age; weight; sex; creatinine concentration; vancomycin doses, duration of infusion and administration times; vancomycin concentration measurements and sampling times. In addition, the clock times when the loading dose and the first maintenance were administered were recorded.

Pharmacokinetic analysis

The clinical characteristics of each patient and their vancomycin dose and concentration data were entered into a MAP Bayesian pharmacokinetic package, OPT.[3] Initial estimates of vancomycin clearance (CL) and volume of distribution (V) were obtained using the Matzke equations[4] assuming a one-compartment model. Creatinine clearance was estimated using the Cockcroft Gault equation.[5] OPT was then used to generate individual estimates of vancomycin CL and V for each patient by combining these initial estimates with the observed concentration data. Any patient whose measured concentrations varied by more than 20% from those predicted using the individual parameter estimates was removed from further analysis. This was done to avoid confounding the results with data from patients with rapidly changing renal function or errors in dose or sample time. The individual pharmacokinetic parameter values were then used to predict vancomycin concentrations at the time the first maintenance dose was administered and at 6, 8, 10, 12 and 14 hours after the start of the correct banded loading dose and after a dose of 20 mg/kg (capped at 3000 mg). The percentages of predicted vancomycin concentrations within the 10 - 20 mg/L target range were then determined for each time point.

Results

A total of 59 patients were initially identified, of which 10 were removed due to poor fits of their data and uncertainty regarding the accuracy of the dose or sample times. The 49 patients included in the final data set comprised 27 males and 22 females. Patients had a mean (SD) age of 63.1 (16.7) years, weight 80.1 (27.6) kg and creatinine concentration 71 (18) µmol/L. Estimated creatinine clearance had a mean (SD) of 91.7 (42.7) mL/min and ranged from 40 to 240 mL/min. All patients received 12 hourly maintenance doses of vancomycin.

Of the 49 patients, 35 (71%) were treated according to the SAPG vancomycin guidelines[2] and were prescribed appropriate loading doses, maintenance doses and maintenance dosage intervals. Loading doses ranged from 750 mg to 2000 mg, (8.1 – 28.8 mg/kg). Five patients (10%) received the wrong loading dose, which was too high in 4 patients and too low in one patient. The maintenance dose was incorrect for 11 patients (22%); 6 received a dose that was too low for their estimated renal function and 5 a dose that was too high. The dosage interval was incorrect for one patient, who was prescribed 24 hourly dosing instead of 12 hourly dosing. It was found that 30 patients (61%) had their first maintenance dose administered between the hours of 11 pm and 7 am. These dose administration times were generally continued for the duration of the vancomycin treatment.

The first maintenance dose was administered at a mean (SD) of 12.8 (1.7) hours after the loading dose. Figure 1 shows the predicted vancomycin concentrations at the actual times patients received their first maintenance dose after loading, based on their individual pharmacokinetic parameter estimates and their loading doses. In summary, 35 (71%) patients received their first vancomycin maintenance dose between 11 and 13 hours after the loading dose, 13 (29%) more 13 hours after loading and 1 less than 11 hours after loading. Predicted trough concentrations were within the target range in 27 patients (55%), above 20 mg/L in 2 (4.1%) patients and below 10 mg/L in 20 (41%) patients.

Figure 2 shows the predicted vancomycin concentrations at various times after the banded loading dose and Table 1 summarises the percentages of concentrations within the target range at these times based on both the banded loading dose and 20 mg/kg. The results show that the optimum time for patients to receive their first maintenance dose is 6-8 hours

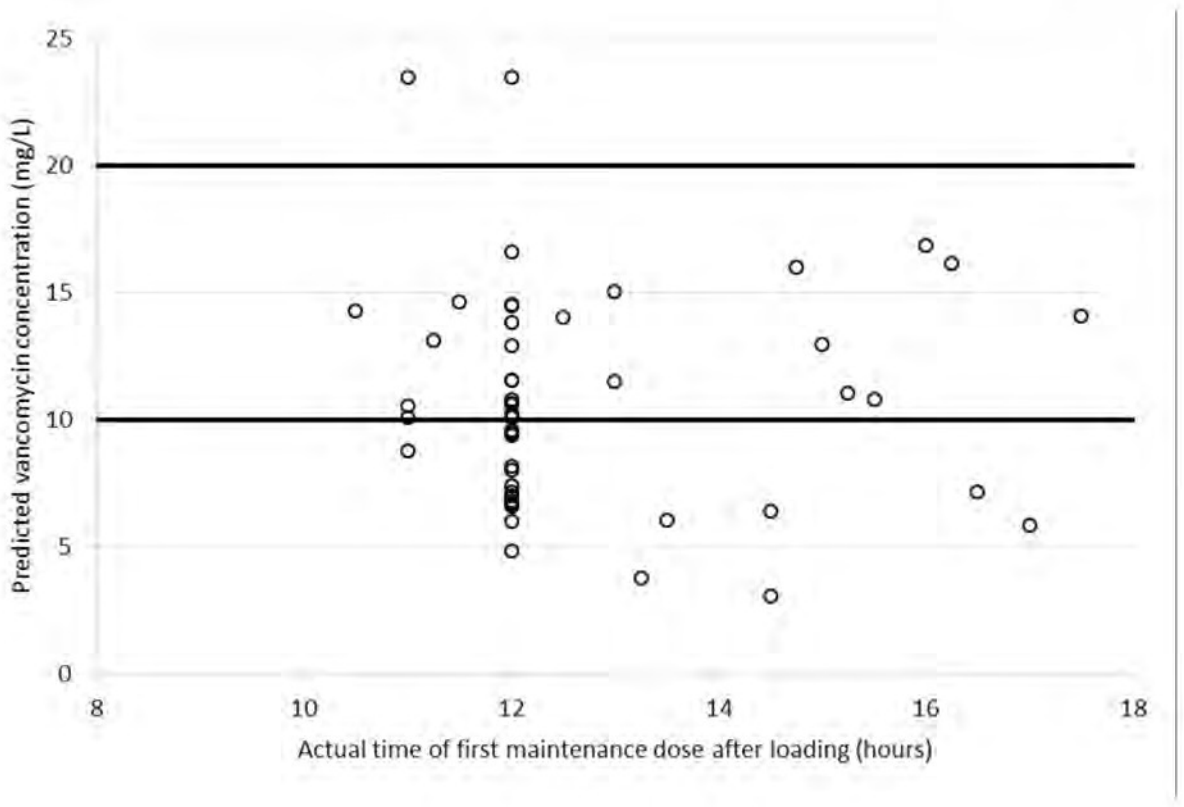

Figure 1: Predicted vancomycin trough concentrations at the times the first maintenance dose was administered. The solid lines indicate the target range of 10-20 mg/L.

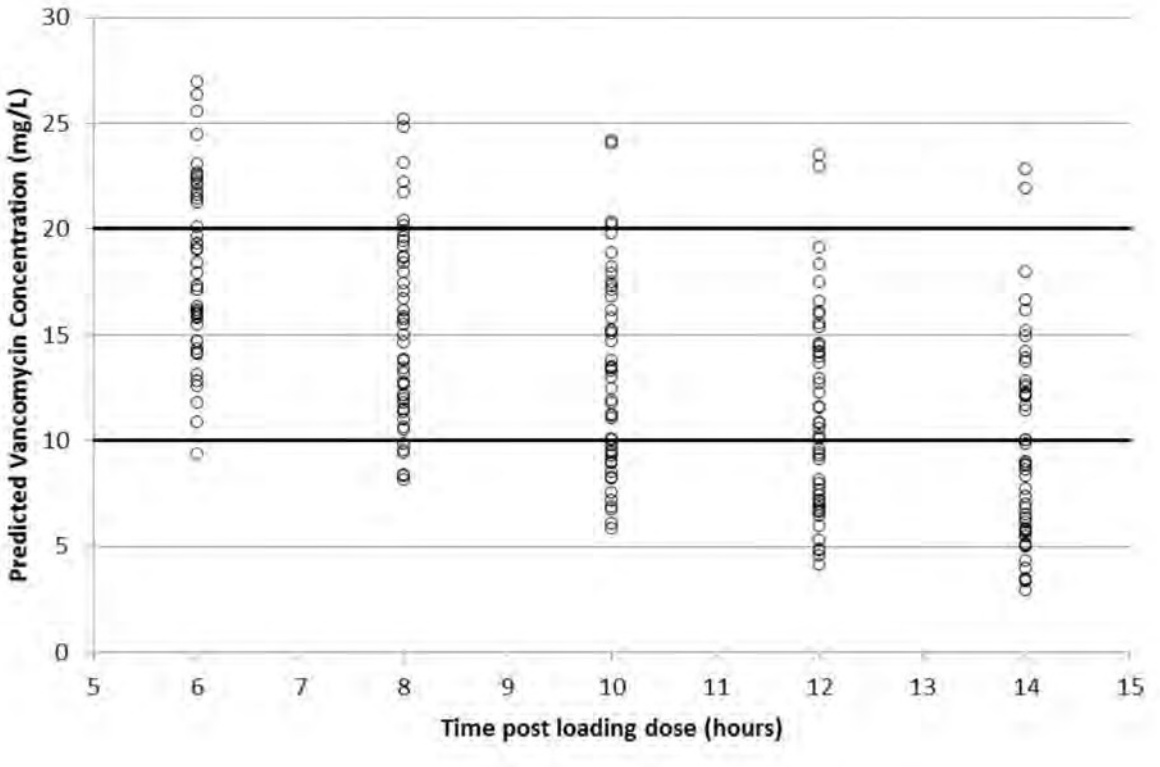

Figure 2: Predicted vancomycin concentrations at various times after a weight-banded loading dose.[2] The solid lines indicate the target range.

after the loading dose, which is associated with 65-74% of concentrations being within the target range with the banded loading dose and 71-84% with 20 mg/kg. Giving the first maintenance dose 14 hours after the loading dose was the worst option, with only 39% of patients within the target range and 57% below 10 mg/L.

Discussion

This audit was conducted to assess whether anecdotal concerns about vancomycin therapy were justified and, if so, whether guidelines could be modified to improve staff and patient convenience and reduce the risk of underdosing. Since almost two-thirds of patients (61%) received their first maintenance dose of vancomycin between the hours of 11pm and 7am, the study confirmed that patients often receive vancomycin doses at times that are inconvenient to staff and disturb patients overnight. These issues arise because decisions to start vancomycin are often made in the late morning or early afternoon and loading doses are therefore administered after midday. The SAPG guidelines[2] currently recommend giving the first maintenance dose at the normal dosage interval, which is typically 12 hours. Consequently, patients are routinely prescribed dosage regimens that require overnight dosing throughout the course of vancomycin therapy.

A second concern was that after loading, trough concentrations were often below the target minimum value. As trough concentrations are not routinely measured after a loading dose, for the purposes of this study, troughs were predicted using pharmacokinetic parameters derived from an individual analysis of data collected from each patient. To reduce the impact of the population model on these predictions, only patients who had at least two concentration measurements and a good fit of their data were included in the analysis. Consequently, higher variability is likely in routine clinical practice.

The results demonstrated that only 52% of patients were likely to have a satisfactory vancomycin trough at the actual time they received their first maintenance dose and even if the next dose had been given at exactly 12 hours after the correct loading dose, this value only increased to 53%. This may partly reflect the use of loading doses banded within weight ranges rather than a mg/kg approach, which was done to simplify the dose calculation and preparation of the infusion.[2] However, using a 20 mg/kg loading dose achieved similar results. Furthermore, a recent systemic review has shown that although starting vancomycin therapy with a weight related loading dose significantly increased the likelihood of achieving target trough concentrations, loading doses did not consistently achieve therapeutic concentrations.[6] A potential solution to this problem is to give a higher loading dose. Rosini et al[7] found that increasing the loading dose from 15 to 30 mg/kg increased the percentage of patients with initial 12 hour troughs above 10 mg/L from 15% to 80%. However, some clinicians expressed concerns that doses above 25 mg/kg might lead to a higher risk of nephrotoxicity. In any case, this approach would not solve the problem of overnight antibiotic administration.

An alternative approach would be to allow more flexibility in the time interval between administration of the loading and first maintenance doses. This is similar to the concept of "multiple loading doses" proposed by Denetclaw et al,[8] who suggested giving 15 mg/kg every 6, 8 or 12 hours over the first 24 hours of therapy, according to renal function. The present study used a higher initial loading dose and focused on the timing of the first maintenance dose only. The results demonstrated that troughs above 10 mg/L were more likely if the first maintenance dose is given 6 or 8 hours after the loading dose and that there was a low incidence of concentrations above 25 mg/L (6% at 6 hours post dose). Delaying the next dose beyond 12 hours after loading gave the worst results. Subsequent maintenance doses would then be given according to the guidelines (usually 12 or 24 hourly) until the dosage interval was confirmed or modified according to measured concentrations. The advantage of this approach is that it allows flexibility in dosing times. If a patient is given a loading dose at 2 pm, they can start regular maintenance therapy at 8 pm or 10 pm rather than having to wait till 2 am. It would be prudent to re-audit practice if any changes are made as a result of these findings. Further research would be welcome to confirm the findings and to assess any unintended consequences e.g. impact on nephrotoxicity or ototoxicity.

Time after loading	Percentage of vancomycin concentrations within range							
	< 10 mg/L		10 – 20 mg/L		20 – 25 mg/L		>25 mg/L	
Hours	Banded	20 mg/kg	Banded	20 mg/kg	Banded	20 mg/kg	Banded	20 mg/kg
6	2	0	65	71	27	27	6	2
8	12	6	74	84	12	10	2	0
10	35	27	57	67	8	6	0	0
12	43	39	53	55	4	6	0	0
14	57	51	39	43	4	6	0	0

Table 1: Percentage of patients whose predicted vancomycin concentrations were within various ranges at different times after the start of a banded or 20 mg/kg loading dose.

Conclusion

The predicted concentrations observed in this audit demonstrate that current practice within the acute hospital setting results in a high proportion of vancomycin maintenance doses being administered at impractical times and risks early subtherapeutic trough concentrations. To reduce this risk and to reduce disruption to patients and staff, vancomycin dosage guidelines could be modified to recommend that the first maintenance dose is administered 6 – 12 hours after the start of the loading infusion.

Declaration of interests

A. Carruthers has nothing to disclose.
Dr. Thomson has nothing to disclose.
Y. Semple has nothing to disclose.
Dr. Rodger has nothing to disclose.

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