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Research Article

Vancomycin Dosing and Pharmacists' Contribution to Therapeutic Monitoring: Single Centre Retrospective Study

Emma McLaren*, Iouri Banakh, Lakmal Wanniarachchi, Sok Leng Cam, Grace Loh, and Darshana Meanger

Department of Pharmacy, Frankston Hospital, Australia

***Corresponding author**

Emma McLaren, Department of Pharmacy, Frankston Hospital, 2 Hastings Road, Frankston 3199, Victoria, Australia, Tel: 061397847601; Email: EMcLaren@phcn.vic.gov.au

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Keywords

- Vancomycin; Therapeutic drug monitoring; Pharmacist; Hospital

Abstract

Background: Vancomycin is an antibiotic with a narrow therapeutic index. Due to this and the need to obtain early effective levels without inducing adverse effects is a clinical challenge. Vancomycin dosing and monitoring guidelines are available from professional societies and hospitals, but the adherence to these has a wide rate of success, including with pharmacists' input.

Objectives: To investigate adherence to vancomycin guidelines, therapeutic drug monitoring (TDM), therapeutic range (TR) attainment and the impact of clinical pharmacists on these parameters.

Method: Single centre, retrospective audit reviewed adults who received vancomycin between 2014-2015. Data was extracted from digital medical records and TDM sheets completed by pharmacists. Adherence to hospital guidelines was analysed for dosing, adjustments for renal function and body weight.

Results: 525 vancomycin courses were reviewed with a mean duration of vancomycin use of 5.1 days with a mean of 2.7 trough levels taken. Pharmacists' involvement in vancomycin therapy resulted in a mean of 1.13 trough levels in TR per patient versus 0.51 ($p<0.001$) without pharmacist involvement, as well as a mean of 1.61 appropriately taken levels versus 1.00 ($p<0.001$). 328 patients had a recorded weight; 160 received a loading dose, 46.9% were under-dosed and 5% were overdosed. Initial maintenance doses were under-dosed in 22.2% patients and overdosed in 13.4% patients. Initial frequency was lower than recommended in 7.6% patients and higher in 21.6% patients.

Conclusion: This study identified that there was low adherence to the hospital's guidelines for vancomycin dosing and monitoring. Pharmacist involvement improved monitoring and TR attainment.

INTRODUCTION

Vancomycin is an antibiotic with a narrow therapeutic index and efficacy against methicillin resistant staphylococcal (MRSA) infections [1-3]. Early use of vancomycin was associated with significant toxicity, including nephrotoxicity, requiring therapeutic dose monitoring to reduce the risk of adverse events. However, there is conflicting evidence regarding the use of serum concentration monitoring to prevent and predict toxicity and efficacy respectively.

On the basis of limited studies (both animal and human) a value of area under the curve (AUC), divided by minimum inhibitory concentration (MIC) of more than 400 has been established as the ideal pharmacodynamic parameter [2]. However, the most practical and accurate method of monitoring vancomycin is through serum trough concentrations. The serum trough concentration is a surrogate marker for AUC and should be obtained just prior to the fourth dose at steady state conditions. Though, it must be noted that "achievement" of steady state concentration is variable and available evidence does not support the monitoring of peak vancomycin serum concentrations as they do not correlate with either efficacy or toxicity [2,4]. Monitoring of trough vancomycin serum concentration is required to reduce nephrotoxicity in patients who are receiving therapy to target serum concentrations of 15-20mg/L, patients who are on prolonged courses (>3-5 days), or those who are at risk of toxicity [2]. Still, the exact frequency of monitoring is often a matter of clinical judgement [2]. Therefore, careful individualisation of vancomycin and judicious use of serum concentration monitoring assists in selecting the appropriate dose and minimising toxicity [4]. Previous international studies indicated poor adherence to guideline based vancomycin use as well as a need for improved practice in therapeutic drug monitoring in Australia and New Zealand [5-7]. Similarly, anecdotal evidence from local practice suggested that vancomycin dosing and therapeutic drug monitoring had a large scope for improvement. Hence, a study of vancomycin dosing, therapeutic drug monitoring (TDM) and pharmacists' impact on these was conducted at our tertiary centre.

METHOD

A retrospective cohort study was conducted examining vancomycin therapy over a 12 month period, from of March 2014 to April 2015, at a tertiary hospital in Victoria, Australia. The method has been described previously [8], but briefly, all patients prescribed vancomycin were included in the study if they were aged greater than 18 years and received more than one intermittent dose of vancomycin, with the therapy initiation at the study site. Patients were excluded from the study if their vancomycin courses were initiated prior to the study period, if they received a continuous infusion or if they were prescribed non-intravenous route of vancomycin. Data was obtained from the hospital's electronic health-record (EHR), and pharmacist completed vancomycin TDM sheets. Scanned digitised medical records were reviewed for each eligible course of vancomycin and for further pharmacist involvement.

Data collected included patient demographics, indications for vancomycin therapy, loading and maintenance doses, dosing frequencies, serum creatinine on admission and at the start of vancomycin treatment, as well as peak serum creatinine while on vancomycin. TDM (guideline adherence and total number of trough levels), duration of vancomycin course, pharmacist involvement (dose adjustments, renal, level, frequency, trough level ordered on the EHR, cessation of vancomycin, microbiology cultures, stewardship, renal impairment, adverse effects, concurrently prescribed nephrotoxic agents) were also collected. Data was recorded in a customised and secured Excel spreadsheet.

The primary outcomes of the study were: proportion of patients commenced with guideline based doses of vancomycin using patients' weight and dosing frequency based on renal function at baseline, proportion of patients treated with vancomycin who had pharmacist involvement, and guideline based vancomycin level monitoring with pharmacist involvement compared to medical management alone. Secondary outcomes were pharmacist TDM contributions: dose and or frequency adjustments, reminders for vancomycin level checks, improvement in number of patients reaching target trough level range, and cessation of therapy if not required based on culture results. Patients who did not have a body weight recorded in the medical records were excluded from dosing and frequency selection analysis. If a patient received more than one course of vancomycin it was considered a separate course if there was greater than 48 hours between doses. A trough level was defined as a serum vancomycin level taken within 1 hour prior to the next due dose for the purpose of this study.

Statistics

The statistical analysis was performed using SPSS 19 with continuous variable analysis using Student t-test or Mann-Whitney U tests after distribution assessment with Smirnov-Kolmogorov test. Bivariate parameters were compared using Chi squared or Fisher's exact test. All p-values below 0.05 were considered statistically significant.

Ethics

The study received an ethics exemption from the study site Human Research Ethics Committee. No funding was obtained for the conduct of the study.

RESULTS

Seven hundred and seventy courses of vancomycin were identified during the study period, of which 525 were eligible for analysis. The most common reasons for exclusion from the study were patients receiving less than or equal to one dose of vancomycin and oral vancomycin use. The average patient age was 63.6years (range 18-98), with 58.1% of patient being male. Most common comorbidities for the population were hypertension, diabetes and malignancy. The mean serum creatinine (SeCr), was 119.8μmol/L prior to initiation of vancomycin with 12.2% of patients having history of chronic kidney disease (Table 1). The most common indications for vancomycin were sepsis (29%), and skin infections (18.1%) [8].

Vancomycin loading doses were administered to 44.4% of patients with a mean dose of 1577mg (500-2500mg). The average maintenance vancomycin dose for the study population was 1118mg (345-2500mg) with a mean frequency of 15 hours

Table 1: Baseline Characteristics of Patients.

Characteristics	Number (525)
Gender Females Males	 220 (41.9%) 305 (58.1%)
Age (years; mean)	63.6 (95%CI 62.0-65.2) (18-98)
Weight (kg; mean) (n=328)	81.9 (95%CI 79.2-84.7) (35-197)
Height (cm; mean) (n=245)	171.4 (95%CI 170.1-172.7) (140-201)
Initial SeCr (μmol/L)	119.8 (34-2162)
Comorbidities Hypertension Ischaemic Heart Disease Congestive Cardiac Failure Atrial Fibrillation Cerebrovascular Accident Transient Ischaemic Attack Peripheral Vascular Disease Gastro-oesophageal Reflux Disease Chronic Renal Failure Chronic Obstructive Pulmonary Disease Malignancy Hypercholesterolaemia Diabetes Obesity Smoker or ex-smoker Depression	 208 (39.6%) 101 (19.2%) 49 (9.3%) 70 (13.3%) 51 (9.7%) 17 (3.2%) 64 (12.2%) 93 (17.7%) 64 (12.2%) 81 (15.4%) 137 (26.1%) 115 (21.9%) 152 (29.0%) 30 (5.7%) 36 (6.9%) 46 (8.8%)
Intensive Care Unit Admission	159 (30.3%)
Vancomycin Initial SeCr at Initiation of VANC (μmol/L) Loading Dose (Courses) Loading Dose (mean; mg) Initial dose (mean; mg) Initial Frequency (mean; hours) Peak SeCr on VANC (μmol/L) Treatment duration (days; mean)	 112.6 (26-943) 233 (44.4%) 1577mg (500-2500) 1118mg (345-2000) 15 (12-72) 129 (28-1528) 5.1 (1-54)

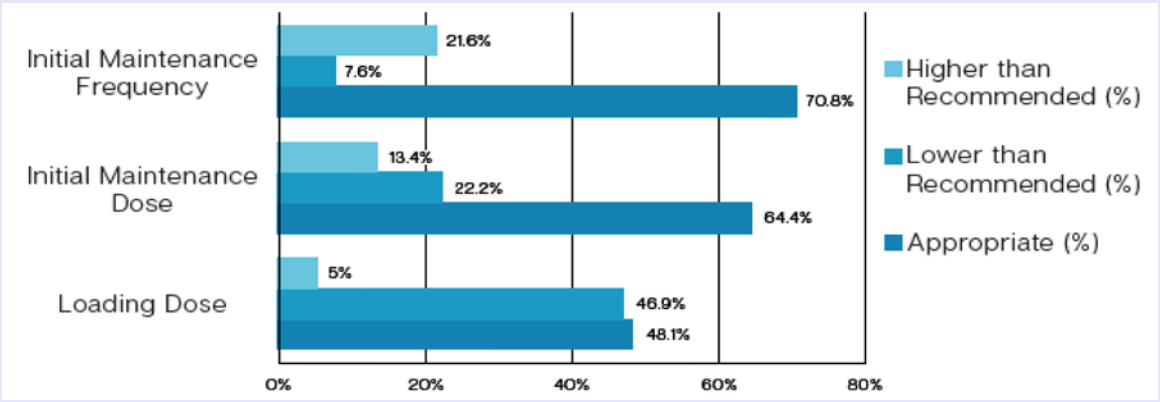

Figure 1 Vancomycin dosing compared to hospital guideline.

(12-72 hours).The mean duration of vancomycin use was 5.1 days (95% CI 4.7-5.5).

Of the 233 patients who were loaded with vancomycin, 160 (69%), patients had a recorded body weight. Based on the vancomycin hospital guideline for loading doses: 5% of patients were given doses above the recommendations, 46.9% patients were given doses below recommendations and 48.1% patients received guideline based doses. Hospital guideline based maintenance doses were prescribed in 64.4% of patients with a recorded body weight, while 13.4% of patients were given doses above and 22.2% were given doses below guideline recommendations. The initial maintenance frequency was lower than recommended by the guideline in 25 (7.6%), patients and higher in 71 (21.6%), patients (Figure 1).

Two hundred and forty three (46.3%), patients had TDM sheets completed by a clinical pharmacist. The most common interventions by pharmacists were the addition of a level reminder to the EHR (23%), followed by dose adjustments (18.9%) (Table 2). Over half (53.0%), of all patients had a guideline recommended TDM level during treatment, with 48.2% of these patients having pharmacist involvement. Pharmacist involvement during therapy was associated with increased rate of guideline recommended TDM, 41.0% versus 77.0% (p<0.001).Therapeutic range was attained on average for 0.8 (0-14) trough levels during the course of vancomycin. 55.2% patients had no trough levels that were in the therapeutic range and 21.5% patients only had one trough level in the therapeutic range. Pharmacist involvement significantly increased the number of therapeutic levels achieved per patient (0.51 versus 1.13 [95%CI -0.91 to -0.37] p<0.001). TDM was conducted with a mean of 2.7 (0-26 [95%CI 2.4-3.0]) trough levels taken per course of vancomycin. Ninety three patients had no trough levels taken during their course of treatment, with 96.8% of these patients having no pharmacist involvement in their management. The mean number of guideline based levels taken during a course of vancomycin in the study period was 1.3 (0-14 [95%CI 1.1-1.4]) per patient. The first trough level taken during treatment occurred after a mean of 2.1 (0-8) doses. Most patients who received loading doses had TDM done, but 15.5% had no levels checked during their treatment. The first trough level taken after vancomycin loading was in-line with the guideline recommendation in 18.8% of patients, of which 43.2% had pharmacist involvement. Inappropriate TDM, with levels taken outside of guideline recommendations occurred in 29.3% patients during the entire treatment, with 76% of these patients having no pharmacist involvement.

Patients who had a vancomycin TDM sheet completed by a clinical pharmacist had been treated with vancomycin for longer on average (4.2 days vs. 6.1 days, p<0.001). Of the 144 patients with an appropriate level who did not have any pharmacist involvement, 14 patients had a vancomycin treatment duration of 1-2 days, 24 patients had a 3 day treatment course, 37 patients had 4 days treatment and the remaining 69 patients had a treatment course greater than 5 (5-28) days.

DISCUSSION

The results of this study showed that there is a high prevalence of non-adherence to hospital guidelines for vancomycin dosing with respect to loading dose, maintenance dosing and frequencies, as well as TDM. This poor adherence translated into low levels of therapeutic target attainment, and low monitoring levels. Compared to previously published Australian studies of vancomycin guideline adherence rates of 51%-63%, our results were similar at 64.4% for maintenance dosing [9,10]. However, our site vancomycin loading rates were higher at 44.4% compared to 28.3% [10].

Many patients at the study site had no recorded interventions from clinical pharmacists, but those who did had a higher

Table 2: Pharmacist Involvement in Vancomycin Therapeutic Drug Monitoring.

Pharmacist Involvement	Rate (%)
Vancomycin TDM Sheet completion	243 (46.3%)
Dose adjustment	99 (18.9%)
TDM level	93 (17.7%)
TDM Renal function	24 (4.6%)
TDM frequency adjustment	31 (5.9%)
Level reminder	121 (23.0%)
Cessation based on culture	11 (2.1%)
Cessation based on stewardship	7 (1.3%)
Cessation due to AKI	1 (0.2%)
Cessation due to AEs	3 (0.6%)
Reason for not administering treatment documented	19 (3.6%)

likelihood of having TDM performed and a greater number of therapeutic levels during their treatment. This type of finding has been observed in other centres where clinical pharmacists' interventions had been implemented [10,11].

The main limitations of this study are: the single site analysis, collection of only written/recorded communications between pharmacists and the medical/surgical teams in regards to dosing and monitoring of vancomycin. Many short-courses of vancomycin, especially those that occurred over periods of reduced pharmacist staffing would have limited opportunity for pharmacists' contributions or have non-recorded contributions such as cessation of therapy recommendations based on microbiological culture results. The study also did not examine the clinical outcome of vancomycin dosing on infection cure rates or patient mortality and morbidity, but nephrotoxicity outcomes have been reported elsewhere [7]. While the study site was single, it examined clinical practices at a tertiary service with over 400 beds with intensive care, surgical and general medical and speciality services. During reduced clinical pharmacist staffing periods there was an established TDM service provided by dispensary staff utilising the pharmacist TDM sheets and antibiotic level reporting system from the local pathology service that would have minimised the impact of reduced clinical pharmacist input.

CONCLUSION

This study has confirmed previous study results and anecdotal suggestion of poor guideline adherence with vancomycin dosing and TDM. While pharmacist involvement has improved both guideline adherence and therapeutic level attainment, significant gaps in practice have been identified and will require systemic improvements to reduce potential patient harm through both supratherapeutic and subtherapeutic vancomycin dosing, and inappropriate prescribing practices.

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