CLINICAL INVESTIGATION

Implementation of Vancomycin Monitoring Criteria in a Pediatric Hospital

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OBJECTIVES The primary objective of this retrospective study was to determine if implementation of vancomycin monitoring criteria could reduce the number of serum vancomycin concentrations obtained without adversely affecting patient outcomes.

BACKGROUND Controversy regarding the correlation between serum vancomycin concentrations and its efficacy and/or toxicity persists. Little evidence has shown a correlation between vancomycin peak concentration (20–40 mg/L) and toxicity. Likewise, there is little information that supports an association between trough (5–15 mg/L) serum concentrations and clinical cure or *in vitro* killing rates. For these reasons, many question the clinical utility and cost-effectiveness of monitoring serum vancomycin concentrations.

METHODS We reviewed medical records of 193 patients (1 d–19 yrs) who received vancomycin during a 2-month period before (Group 1; n = 100) and after (Group 2; n = 93) implementation of vancomycin monitoring criteria.

RESULTS There was no difference ($P > 0.05$) in baseline age, weight, white blood cell count, temperature, serum creatinine, and blood urea nitrogen between Groups 1 and 2. Although 49.5% of all patients had vancomycin serum concentrations performed, significantly ($P < 0.005$) fewer patients in Group 2 (32%) were monitored when compared to Group 1 (65%). Peak serum vancomycin concentrations were within the reference range (20–40 mg/L) in 48% of patients in Group 1 compared to 80% in Group 2 ($P = 0.03$). The mean duration of vancomycin therapy was greater ($P = 0.004$) for patients in Group 1 (7 ± 7.5 days) compared to Group 2 (4 ± 4.4 days) and the medians for the two groups were also different. Mean ending temperatures ($P = 0.23$), white blood cell counts ($P = 0.71$), serum creatinine ($P = 0.3$) and BUN ($P = 0.24$) were not different for the two groups.

CONCLUSIONS Implementation of criteria to decrease unnecessary serum vancomycin concentration monitoring does not adversely affect patient outcome and may decrease cost to the institution, healthcare system, and patient.

KEYWORDS: serum concentrations, therapeutic drug monitoring, vancomycin

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INTRODUCTION

Despite widespread use of vancomycin for decades, controversy regarding the need to monitor vancomycin peak and trough serum concentrations persists.[1-4] Little evidence supports a correlation between vancomycin peak (20–40 mg/L) serum concentrations and toxicity.[5-8] Likewise, there is little support that a correlate exists between clinical cure or *in vitro* killing rates and trough (5–15 mg/L) serum vancomycin concentrations.[8,9] For these reasons, the clinical utility and cost-effectiveness of monitoring these concentrations remains questionable.

ABBREVIATIONS: Group 1, 2 months before criteria were implemented; Group 2, 2 months after criteria were implemented

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Table 1. Vancomycin Monitoring Criteria

Vancomycin concentrations are indicated in the following situations:

• Trough	Young infants (≤ 3 months)
• Trough	Critically ill patients (e.g., concurrent organ dysfunction)
• Trough	Patients with renal dysfunction/failure based on elevations in serum creatinine above the age-related reference range
• Trough	Patients receiving concurrent nephrotoxic drugs (e.g., amphotericin B, cyclosporine)
• Trough	Patients receiving unusually large doses (e.g., > 60 mg/kg/day or ≥ 4 gm/day) to include patients with CNS infections and endocarditis
• Peak/Trough	Burn patients
• Peak/Trough	Patients who are not clinically responding by 72 hr or who have persistent (+) cultures

Unless vancomycin will be continued for ≥ 72 hrs, serum vancomycin concentrations should not be arbitrarily ordered when vancomycin is prescribed.

It has been clinical practice at our pediatric institution for physicians to routinely order (e.g., after 3rd dose) peak and trough serum vancomycin concentrations concurrent with the initiation of vancomycin. Such practice is frequently done without regard for the need for such monitoring and without consideration for the expected duration of vancomycin therapy. It has also been our experience, and the experience of others,[10-13] that age-related normal doses of vancomycin generally produce serum concentrations within the accepted reference ranges when administered to normal, otherwise healthy infants ≥ 3 months of age and children. Since concentration values within the accepted reference range are usually achieved, the practice of routinely monitoring serum vancomycin concentrations appears to be both clinically unnecessary and economically burdensome. The objective of this study was to determine if implementation of monitoring criteria would reduce the number of unnecessary vancomycin serum concentrations without adversely affecting patient outcomes.

METHODS

Vancomycin monitoring criteria were developed jointly by the Pharmacokinetic Service and by a member of the Infectious Diseases Service of our hospital. The Infectious Diseases Division, the Pharmacy and Therapeutics Committee, and the Medical Staff Executive Committee of our institution approved the criteria (Table 1). Although developed by our institution, the vancomycin monitoring criteria that we employed have been previously published by another group.[13] This study was approved by the Institutional Review Boards of The University of Tennessee Health Science Center and Le Bonheur Children's Medical Center, and informed consent was deemed unnecessary.

Before implementation of these criteria, the Pharmacokinetic Service did not intervene until a blood sample had been collected and the laboratory had reported a concentration. Following implementation of the criteria, the unit secretary contacted the Pharmacokinetic Service when an order for serum vancomycin concentration(s) was written. The Pharmacokinetic Service then used the criteria to evaluate the appropriateness of the order and either approved or canceled the serum vancomycin concentration(s).

Medical records were reviewed for all patients who received vancomycin during a 2-month period before (Group 1) and after (Group 2) implementation of the criteria. Demographic data including age, weight, diagnosis, and vancomycin dosing were collected. Peak serum concentrations were collected 1–1.5 hours after the end of the infusion via syringe pump and trough concentrations were obtained 30 minutes before the end of the dosing interval. The type of serum vancomycin concentration (e.g., peak, trough), the reported value(s), and time and duration of medication administration were also recorded. Additionally, baseline temperature, white blood cell (WBC) count, serum creatinine (SCr), and blood urea nitrogen (BUN) were recorded. In order to determine if decreased monitoring of serum vancomycin concentrations (implementation of the criteria) adversely affected patient outcomes (efficacy or toxicity), mean post-vancomycin WBC count, temperature, and duration of vancomycin therapy before and after initiation of the criteria were compared. Differences in adverse effects before and after implementation of the criteria were evaluated by assessing changes in mean SCr and BUN. We were unable to assess ototoxicity since our institution does not routinely perform auditory studies in patients receiving this medication. Likewise, our institution does not have an

Table 2. Patient Characteristics

	Group 1 (n = 100)	Group 2 (n = 93)	P value
BASELINE			
Age (yrs)	4.1 ± 4.9	3.6 ± 4.7	0.42
Weight (kg)	15.3 ± 16.7	15 ± 16	0.91
Vancomycin (mg/kg/day)	36.9 ± 10.3	37.7 ± 9.9	0.7
Temperature (°C)	37.5 ± 1.5	37.4 ± 1.2	0.6
WBC (1000 /μL)	14.1 ± 7.9	13.3 ± 7.8	0.49
SCr (mg/dL)	0.5 ± 0.3	0.7 ± 0.9	0.06
BUN (mg/dL)	12 ± 8.8	16 ± 17	0.09
POST-VANCOMYCIN			
Temperature (°C)	36.9 ± 0.6*	37.0 ± 0.6*	0.23
WBC (1000/mm²)	13.9 ± 8.5	13.4 ± 9.5	0.71
SCr (mg/dL)	0.7 ± 1.1	0.5 ± 0.7*	0.3
BUN (mg/dL)	22 ± 36	16 ± 18	0.24

** = P < 0.05, baseline vs. post-vancomycin.*

Oncology Service; therefore, patients with cancers are not represented in this study.

There were two questions we hoped to address using data analysis. The first was to assess *predictive use* of the criteria (i.e., should the patient have been monitored). This determined, regardless of whether or not the child was monitored, if the criteria would have required that serum concentration(s) be obtained. The second question assessed whether or not the criteria were appropriately used when serum concentrations were *actually* obtained. Differences in continuous variables between groups were compared using an unpaired Student *t*-test and changes within groups were assessed using a paired-sample *t*-test. Chi-square test was used to compare categorical data. All data are presented as mean ± SD. Significance was set *a priori* at $P \leq 0.05$. Analysis was performed using the MINITAB 13 statistical software (Release 13. Minitab, Inc.)

RESULTS

Demographic data

During the 2-month period before (Group 1; n = 100) and after (Group 2; n = 93) initiation of the criteria, 193 patients were evaluated (Table 2). Mean age was 3.9 ± 4.8 years; median age was 1.4 years, range 1 day to 19 years. Thirty-two neonates were included in the study (14.6 ± 13 days). There were no statistically significant differences in baseline characteristics between Group 1 and Group 2 for age, weight, daily vancomycin dose, temperature, WBC count, SCr, and BUN. Likewise, there were no statistically significant differences in any of the above baseline variables in neonates in Group 1 (n = 13) compared to Group 2 (n = 19).

The predominant admitting diagnoses involved infectious (n =72) and cardiovascular (n = 33) events. Other diagnoses included gastrointestinal surgery (n = 20), pulmonary disease (n = 17), central nervous system surgery (n = 15), trauma (n = 11), renal disease (n = 6), sickle cell disease (n = 3), and other (n = 16). More patients in Group 1 suffered from trauma (n = 10) than in Group 2 (n = 1). While 56% of all patients were admitted to the intensive care unit (ICU), there was no difference in ICU admissions between Group 1 (57%) and Group 2 (56%).

Post-vancomycin temperature, WBC count, SCr, and BUN were not statistically different ($P > 0.05$) between the two groups (Table 2). When comparing baseline and post-vancomycin parameters within each group, a decrease in temperature was noted for each group. SCr was decreased within Group 2. While statistically significant, the changes in temperature and SCr were not clinically important. Duration of vancomycin for all patients was 5.55 ± 6.22 days (range 1-45 days). Length of therapy in Group 2 (4 ± 4.2 days, range 1–21 days) was significantly shorter (P = 0.004) than Group 1 (7 ± 7.5 days, range 1–45). Likewise, the medians were statistically different (P = 0.002). There were no statistically significant differences ($P > 0.05$) in post-vancomycin temperature, WBC count, SCr, and BUN between neonates in Groups 1 and 2 or neonates within each group.

Predictive use of the monitoring criteria

Predictive and actual monitoring data are presented in Table 3. Thirty percent of patients in Group 1 (n = 100) and 26% of those in Group 2 (n = 93) met criteria and should have been monitored following 72 hours of vancomycin. Only two patients in each group should have had both a peak and a trough concentration; 28 patients in Group 1 and 22 in Group 2 should have had a trough concentration obtained. Twelve patients in Group 1 and 15 in Group 2 had multiple criteria for monitoring. The majority of patients in both groups were either critically ill (n = 32), ≤ 3 months of age (n = 26), receiving at least one nephrotoxic medication (n = 14) or displaying signs of renal dysfunction (n = 15). Although there were no statistically significant differences between the two groups for critical illness, age ≤ 3 months, and concurrent nephrotoxic medica-

Table 3. Predictive versus Actual Serum Vancomycin Concentration Monitoring Using the Approved Criteria*

	SERUM VANCOMYCIN CONCENTRATION MONITORING		
	Peak and Trough n (%)	Peak only n (%)	Trough only n (%)
Predictive monitoring† *(n = 54)*			
Group 1 (n = 30)	2 (6.7)	0	28 (93.3)
Group 2 (n = 24)	2 (8.3)	0	22 (91.7)
Actual monitoring (n = 95)			
Group 1 (n = 65)	48 (73.8)	6 (9.3)	11 (16.9)
Group 2 (n = 30)	9 (30.0)	1 (3.3)	20 (66.7)

*Table 1.
†should have been monitored following 72 hours of vancomycin.

tions, significantly more patients in Group 2 had renal failure (P = 0.04). The mean ± SD vancomycin dose was 37.26 ± 11.6 mg/kg/day (9.6–64 mg/kg/day). Only two patients in Group 2 received a large dose of vancomycin (> 60 mg/kg/day). One patient in Group 2 had a significant burn injury, and two patients in Group 1 and one in Group 2 were not clinically responding based upon clinical judgement of the child's physician.

Actual use of the criteria

Ninety-five patients (49.2%) had a total of 152 serum vancomycin concentrations measured (Table 3). A total of 113 concentrations were obtained in 65 patients in Group 1 compared to 39 serum concentrations obtained in the 30 patients in Group 2 (P < 0.001). There was a statistically significant difference in the number of serum vancomycin concentrations that were obtained in Group 1 (n = 113) compared to Group 2 (n = 39). Table 3 depicts data showing a significant difference between Group 1 and Group 2 in the number of peak/trough concentrations (P < 0.001) and trough concentrations (P = 0.03). However, there was no statistically significant difference in the number of peak concentrations between the two groups.

Peak serum vancomycin concentrations were within the reference range (20–40 mg/L) in 48% of patients in Group 1 compared to 80% in Group 2 (P = 0.05). Trough serum vancomycin concentrations were within the reference range (5–15 mg/L) in 78% of those in Group 1 compared to 52% in Group 2 (P=0.01). Twenty-one of the 32 neonates (65%) had a peak concentration drawn, 95% of which were between 20–40 mg/L. Trough concentrations were obtained in 62% of these newborns and 65% were within the reference range of 5–15 mg/L.

When the two groups were combined, only 64% of the 95 patients who actually had serum vancomycin concentrations obtained met the monitoring criteria *at the time* vancomycin was prescribed. There was a statistically significant difference between Group 1 (54%) and Group 2 (83%) patients who initially met the monitoring criteria (P < 0.001). Despite meeting the criteria at this time, about 40% of these patients (Group 1 = 31%, Group 2 = 48%) had their vancomycin discontinued prior to 72 hours.

DISCUSSION

Vancomycin is routinely discussed as though the concentrations at which efficacy and toxicity occur are well established. The original determination of the reference range was based on steady-state concentrations produced by a normal adult dose of 2 grams every 12 hours.[3] There is no documentation that concentrations above the reference range will consistently produce toxicity or that concentrations below the reference range will not be clinically efficacious. However, it may be assumed that since vancomycin has time-dependent killing, prolonged periods below the MIC of the organism may result in decreased efficacy.[9] Most recommendations for routine monitoring are based on maintaining concentrations within specified ranges and not on patient outcomes. Despite the above information, routine monitoring of serum vancomycin concentrations remains the standard of practice in many pediatric institutions.

Previous authors have questioned the need for serum vancomycin concentration monitoring in "normal" patients receiving age-appropriate doses.[1-4,8] These commentaries have often excluded pediatric patients from the "normal" population that may not need concentration monitoring. The landmark study that established pediatric dosages recommended that peak concentra-

Table 4. Literature Comparison of Recommendations for Monitoring Vancomycin in Pediatric Patients

CRITERIA FOR SVC MONITORING	REFERENCE (n)				
	10 (n = 209)	11 (n = 74)	12 (n = 82)	13 (n = 129)	CURRENT STUDY (n = 193)
Duration of therapy	*	*	*	†	†
Age					
< 30 d (all patients routinely)	P/T‡	P/T	§	T	T
≥ 30 d (all patients routinely)	NR	T	T	NR	NR
Burns	*	††	P/T‡‡	T‡	P/T
Cancer	P/T	††	P/T	NR	§
Clinically not responding or persistent ⊕ cultures	††	*	P/T‡‡	*	P/T
Critically ill	††	*	P/T‡‡	T‡‡	T
Concomitant nephrotoxins	P/T‡	T	P/T	T	T
Endocarditis	*	*	*	P/T	T
Large dose for age/weight	P/T‡	*	*	T‡	T
CNS infections (e.g., meningitis, ventriculitis)	*	††	P/T	P/T	T
Renal dysfunction-abnormal function	P/T‡	††	P/T	T	T
SERUM CREATININE	Baseline & Weekly	*	Weekly	Weekly	Baseline

SVC, serum vancomycin concentration; P/T, peak and trough serum vancomycin concentration; T, trough serum vancomycin concentration; NR = not recommended provided normal doses for age.
**No specific recommendation made.*
†Provided renal function is normal, serum concentrations should only be obtained when confirmed that vancomycin will continue for a minimum of 72 hr.
‡Although a recommendation is made for monitoring, it is based on experience or medical literature and population or factor was not specifically studied.
§Not included in study.
††Although a suggestion is made for monitoring it is based on experience or medical literature and population or factor was not specifically studied.
‡‡Unable to determine if study included patients with this disease/factor.

tions be obtained to assure that therapeutic concentrations are achieved;[14] however; this study was published before it was known that vancomycin demonstrates time-dependant, not concentration-dependant, killing. Four other reports make specific recommendations for vancomycin concentration monitoring in the pediatric population (Table 4).[10-13]

Thomas et al. assessed serum vancomycin concentrations in patients > 60 days of age receiving normal age-appropriate vancomycin doses for various presumed or documented infections.[10] The authors focused their efforts on evaluating a subset of infants and children with cancers. They noted that the majority of peak and trough vancomycin concentrations were adequate in children without cancer; however, 90% and 79% of patients with cancer had low peaks and troughs, respectively. Although this study did not include neonates, they recommended that peak and trough concentrations be routinely monitored in this population. They also recommended that peak and trough serum concentrations be considered in patients with cancer, in those receiving concurrent nephrotoxic medications (i.e., aminoglycosides), patients with abnormal renal function, and those receiving > 40 mg/kg/day of vancomycin. The authors also suggested that practitioners should consider individualizing doses using peak and trough concentrations based on degree of illness, poor clinical response or persistent positive cultures. The investigators concluded that routine monitoring of serum vancomycin concentrations is unnecessary in children with normal renal function who are receiving normal doses for age.

In a study of pediatric patients receiving normal doses of vancomycin, 5 of 30 neonates had trough serum vancomycin concentrations < 4 mg/L and 16 of 44 infants and children had trough concentrations that were below the lower end of the reference range.[11] No patient had a peak concentration > 60 mg/L. These authors concluded that obtaining a single trough concentration after 1 to 2 days might identify infants and children at risk for inadequate therapy (i.e., low concentrations). Although not supported by their data, they also suggested that neonates should continue to have both peak and trough concentrations monitored.

Lee et al. evaluated vancomycin serum concentrations before and after establishing guidelines

for vancomycin monitoring in pediatric patients outside the neonatal period.[12] Prior to initiating the guidelines, 27% of trough concentrations were < 5 mg/L and 8% were > than 15 mg/L. Of 148 trough concentrations between 5–15 mg/L, 14% were associated with peak concentrations > 40 mg/L. Overall, 3% of the peak concentrations were > 60 mg/L. After implementing their guidelines only 9% of peak concentrations were > 40 mg/L when the trough was between 5–15 mg/L and only 2% were > 60 mg/L. Significantly fewer peak concentrations were obtained after guideline initiation. Bacteriological efficacy was not assessed. The authors concluded that implementing monitoring guidelines results in significant cost savings, and routine monitoring of serum vancomycin concentrations is unnecessary.

Another study assessed the effect of implementing guidelines for monitoring serum vancomycin concentrations in pediatric patients between 7 days and 23 years of age.[13] Guideline implementation decreased the number of concentrations obtained by approximately 86%. There was no difference in the length of time until defervescence, normalization of WBC count, and time until negative blood cultures when comparing the time periods before and after guideline implementation. A decrease in monitoring did not affect SCr or BUN. No patients had documented ototoxicity; however, audiometric testing was not performed. Approximately one third of the patients who received vancomycin had positive blood cultures; however, it is of interest that the time until negative cultures was not affected by decreased serum concentration monitoring.

After initiating our monitoring criteria, patients who had serum vancomycin concentrations obtained decreased by approximately half and the number of concentrations decreased by approximately two-thirds. Interestingly, the type of serum concentration obtained was also affected. About 70% of serum concentrations obtained before use of the criteria were combination peak and trough compared to less than half that number following implementation of the criteria; a trough only concentration became the predominate type of monitoring when the criteria were employed.

Implementing criteria for vancomycin monitoring in our institution decreased the degree of monitoring but did not change the overall appropriateness of monitoring. Since short-term therapy is difficult to anticipate, waiting until the third day of antibiotic treatment for serum concentration monitoring may be more appropriate in most patients than the routine assessment after the third dose. Both our study and that of Chicella et al. required that patients receive a minimum of 72 hours of vancomycin before the monitoring criteria could be applied.[13] This is an essential component to any monitoring protocol and is reinforced by our finding that about a third of patients who met criteria for monitoring at initiation of therapy had vancomycin discontinued prior to 72 hours.

We also noted a decrease in the mean length of vancomycin therapy after the criteria were implemented. While this study was not designed to assess factors that might have contributed to this outcome, it is plausible that the Pharmacokinetic Service aggressively monitored cultures and sensitivities and suggested either vancomycin discontinuation or alternative therapy. Future studies are needed to address the effect of service intervention on the duration of vancomycin therapy.

With the exception of Chicella et al., all other pediatric reports evaluated a dosage's ability to produce serum vancomycin concentrations within the reference range and failed to assess response to therapy independent of concentration.[13] The main objective of our study was to determine if implementation of monitoring criteria would reduce the number of unnecessary vancomycin serum concentrations without adversely affecting patient outcomes. Implementing vancomycin monitoring criteria, thereby decreasing the number of concentrations performed, had no effect on infection parameters (i.e., WBC count, temperature) or renal function (i.e., SCr, BUN). We were unable to assess ototoxicity because audiometric testing is not routinely performed at our institution.

One limitation of our study was the inclusion of all patients receiving vancomycin, regardless of positive cultures documenting the need for vancomycin. To date, pediatric studies have included patients with uncertain infectious diagnoses.[10-13] It is unknown if patients with documented infections also respond as well to age-appropriate dosing with limited serum concentration monitoring. Ideally, a trial including only patients with cultures positive for bacteria requiring vancomycin and randomized to either standard monitoring or to monitoring based on specific criteria should be performed.

Even with monitoring criteria in place, only 83% of patients in whom concentrations were actually obtained met the criteria. Based on the results of this study we have changed the operations of our pharmacokinetic service. The major reason we failed to achieve 100% compliance with the criteria was related to the manner in which orders were placed into the computer system. When the criteria were implemented the pharmacokinetic service depended upon the floor secretary to notify the service when vancomycin concentrations had been ordered by a physician. This chain for notification was not always successful and the floor secretary would simply order the test in his/her computer. Currently, the service prospectively monitors the clinical status of all hospitalized patients who receive vancomycin on a daily basis. The unit secretary can no longer access the laboratory-based computer system to order vancomycin concentrations. Only the pharmacist on the Pharmacokinetic Service has authority to order serum vancomycin concentrations in the computer system for patients who meet the established monitoring criteria. The pharmacist also has the authority to cancel physician orders for vancomycin concentrations that are outside the approved indications.

CONCLUSIONS

Based on our study and other pediatric studies, routine monitoring (i.e. peak and trough after the third dose) of vancomycin concentrations is unnecessary in pediatric patients with normal renal function who are receiving age-appropriate doses. Until additional studies are performed, certain subsets of patients (e.g., neonates; critically ill; thermal injury; cancer; clinically unresponsive or persistently positive cultures; renal dysfunction; administration of concurrent nephrotoxic medications; and requirement for large dose) may require monitoring. With the exception of patients with renal dysfunction or thermal injury, concentrations should not be obtained until 72 hours of vancomycin has been administered. When concentrations are indicated, our current reference range for serum vancomycin concentrations are a peak $\leq$ 40 mg/L and a trough concentration between 5–15 mg/L. Although vancomycin accumulation (i.e., risk for toxicity) is best assessed via a peak concentration, it is difficult to accurately obtain these in the clinical environment. For this reason many studies have recommended a trough concentration to assess the possibility of toxicity. The practitioner should remember that a small percentage of patients with trough concentrations within the reference range have been reported to have concurrent peak concentrations above 40 or 60 mg/L. Although it is not standard practice in our institution, we would advocate obtaining a serum creatinine at baseline and weekly thereafter.

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