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CLINICAL INVESTIGATION

An Assessment of Vancomycin Pharmacokinetic Variability in Pediatric Cardiology Patients

Karen F. Marlowe, PharmD,[1,2] Michael F. Chicella, PharmD,[1,3] Tamara E. Claridge, PharmD,[4] and Susan W. Pittman, BSPharm[5]

[1]Departments of Pharmacy Practice, Auburn University, Auburn, Alabama, Department of [2]Internal Medicine and [3]Pediatrics, University of South Alabama, Mobile, Alabama, [3]Department of Pharmacy, Cincinnati Children's Hospital and Medical Center, Cincinnati, Ohio, [4]Department of Pharmacy, Clarian Hospital, Indianapolis, Indiana, [5]Department of Pharmacy, Egleston Children's Hospital; Atlanta, Georgia

Objectives To establish the steady-state pharmacokinetic profile of vancomycin in pediatric cardiology patients; determine an empiric vancomycin dose; and evaluate the correlation between fluid balance and volume of distribution (Vd), serum creatinine and clearance (CL), and daily dose of furosemide and Vd.

Methods Retrospective pharmacokinetic evaluation in 36 pediatric cardiology, cardiac surgery, or cardiac transplant patients treated with vancomycin. The pharmacokinetic profile for vancomycin including elimination half-life (t1/2), elimination rate constant (ke), volume of distribution (Vd), and clearance (CL) was calculated for each patient. The relationship between fluid balance and Vd, serum creatinine and CL, and the total daily dose of furosemide and Vd was evaluated.

Results The patient population had an average half-life of 5.9±1.2 hr and a Vd of 0.4±0.12 L/kg. A statistically significant correlation was noted between serum creatinine and CL (r^2=0.19, P<0.01). Additionally, a statistically significant correlation exists between the total daily furosemide dose and the Vd (r^2=0.31, P<0.01). A dose of 10 mg/kg/dose every 12 hrs was predicted to result in the greatest number of serum vancomycin concentrations within the reference range.

Conclusions Routine monitoring of serum vancomycin concentrations is prudent for this population, and special consideration should be given to those with elevated serum creatinine and to those receiving large doses of furosemide.

Keywords: Vancomycin, pharmacokinetics, cardiology, pediatrics

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INTRODUCTION

The pharmacokinetic profile of vancomycin has great variability in infants and children.[1,2] Although routine assessment of vancomycin serum concentrations has become less common, certain clinical situations that altered the volume of distribution (Vd) for vancomycin, the presence of renal insufficiency, and / or the concomitant use of nephrotoxic agents warrant the monitoring of serum vancomycin concentrations. The pediatric cardiology population is one group of patients with the potential for the presence of each of the above scenarios or a combination of them. The purposes of this study were to: 1) establish the steady-state population pharmacokinetic parameters of vancomycin in pediatric cardiology patients; 2) determine an empiric vancomycin dose for pediatric cardiology patients that results in serum vancomycin concentrations within the reference range; 3) evaluate the correlation between fluid balance and Vd, serum creatinine and clearance of vancomycin (CL); and 4) assess the relationship between the daily dose of furosemide and the Vd of vancomycin.

Address correspondence and reprint request to Karen F. Marlowe, PharmD, 9 Paddock Drive, Fairhope, Alabama 36532 e-mail: auburn.edu

MATERIALS AND METHODS

Patients at Egleston Children's Hospital who received vancomycin between January 1999 and December 2000 were retrospectively identified through pharmacy records. All patients ≤10 years of age who received intravenous vancomycin and were admitted to the cardiac surgery, cardiology, or cardiac transplant services were included in this analysis. Exclusion criteria included patients with renal insufficiency (i.e., serum creatinine >2 x the upper limit of age-related normal values); patients whose vancomycin serum concentrations were sampled prior to the third maintenance dose; patients whose medical records did not indicate the time of administration; or dosing times were inconsistent with the prescribed intervals.

The initial vancomycin dosage regimen was selected by the prescribing physician. Doses were prepared by the pharmacy, and infused via syringe pump over 60 minutes. Data were collected on the day of serum vancomycin concentrations monitoring and included: vancomycin dose (mg/kg), dosing interval (hours), vancomycin peak and trough serum concentrations (mg/mL), serum creatinine (mg/dL), BUN (mg/dL), the previous day's fluid balance, and total furosemide dose for the previous 24 hours.

Trough serum vancomycin concentrations were collected just prior to a dose. In order to ensure complete distribution, peak concentrations were drawn 60 minutes after the end of the infusion of vancomycin. Reference ranges for peak and trough serum vancomycin concentrations were 20–40 μg/mL and 5–10 μg/mL, respectively. Serum vancomycin concentrations were measured by the clinical laboratory of our institution. Samples were analyzed using fluorescence polarization immunoassay (TDx, Abbott Diagnostic Division, Abbott Park, IL), with a between- and within-day coefficient of variation of <5%.

Data collected at the time of admission included patient gender, weight, age upon admission, baseline serum creatinine and BUN, and the indication for vancomycin therapy. Pharmacokinetic parameters for vancomycin including elimination half-life (t1/2), elimination rate constant (ke), volume of distribution (Vd), and clearance (CL) were calculated for each patient. The ke and Vd were calculated using a one compartment model. Pharmacokinetic parameters were determined for the overall study population and for three subgroups that were stratified according to age. The three groups were neonates (<30

Figure 1. Fluid Balance and Vd

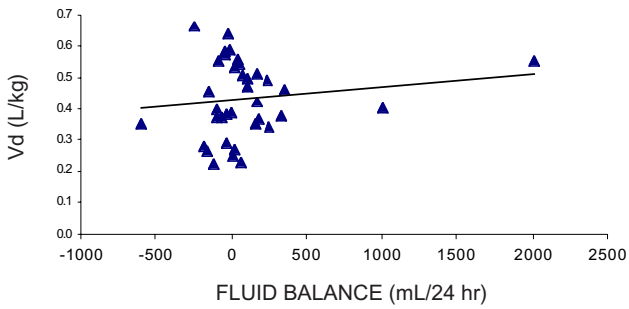

Figure 2. Vancomycin Clearance and Serum Creatinine

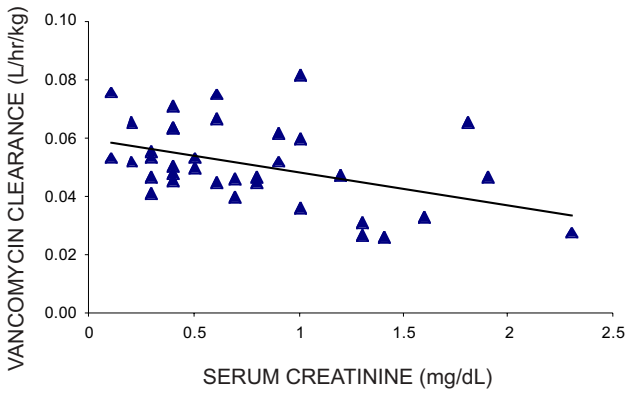

Figure 3. Furosemide and Vd

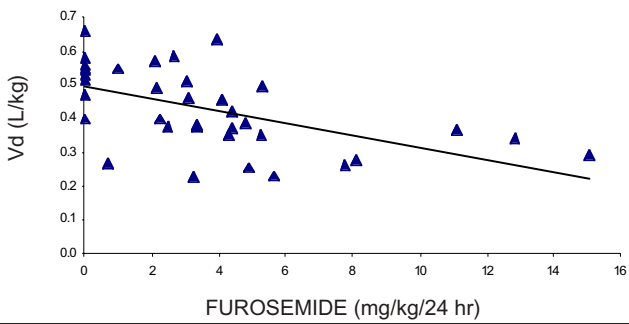

Table 1. Patient Demographics

	Population (n=36)	Neonate (n=14)	Infant (n=13)	Child (n=9)
Age	19.4 mo*	20.7±6.6 d	3±5.2 mo	5.1±2.9 yr
Weight† (kg)	9.3 ± 8.4	3.8 ± 0.6	7.02 ± 2.6	20.23 ± 10.1
Gender				
male (%)	19 (53)	6 (43)	5 (38)	6 (67)
female (%)	17(47)	8 (57)	8 (62)	3 (23)
SCr† (mg/dL)	0.8±05	0.7±0.4	0.7±0.6	0.9±0.5
BUN† (mg/dL)	22±11	24±11	19±11	23±12

** = age range (11 days-10 years); † = mean±SD*

days), infants (1–24 months), and children (2–10 years). The extrapolated serum peak concentration (i.e., the end of the infusion) was used to estimate the Vd. Clearance was calculated as the product of ke and Vd.

Unless otherwise noted, all data are presented as mean ± standard deviation. Linear regression analysis was used to assess the relationship between fluid balance and Vd, and CL. It was also used to assess the relationship between the total daily dose of furosemide and Vd. Correlation was determined between the variables using Pearson's correlation coefficient. In the study, a P value ≤0.05 was considered statistically significant.

Table 2. Population Pharmacokinetic Parameters Based on Initial Vancomycin Dose

	Population*	Neonate*	Infant*	Child*
Dose (mg/kg/dose)	14.7±5.52	14.7± 6.94	13.3±4.33	16.7±4.41
Ke (hr-1)	0.12±0.02	0.11±0.02	0.13±0.03	0.12±0.01
t 1/2 (hr)	5.94±1.23	6.28±1.22	5.78±1.53	5.64±0.56
Vd (L/kg)	0.43±0.12	0.46±0.13	0.41±0.12	0.42±0.1
CL (L/hr/kg)	0.0513±0.14	0.0515±0.0158	0.0504±0.0124	0.0524±0.14

**Mean±SD*

RESULTS

Fifty-five patients received vancomycin during the study. Nineteen patients were excluded for the following reasons: vancomycin for <1 day (n=10), serum concentrations drawn prior to steady-state (n=3), serum concentrations collected after a missed dose (n=3), and serum concentrations obtained around a dose that was more than 1-hour late (n=3). Thirty-six patients, ages 11 days to 10 years, were included (Table 1). Eight (22%) of the patients received vancomycin as prophylaxis for postoperative infection, 11 (31%) for empiric treatment of presumed infection, and 8 (22%) for treatment of documented infection. Nine (25%) of the patients did not have an indication for vancomycin listed in the medical record.

Initial vancomycin dosing ranged from 10–25 mg/kg/dose, and the interval ranged from 8–24 hours. Only eleven patients (30%) had both peak and trough serum vancomycin concentrations within the reference range using this approach. The population pharmacokinetic parameters based on these concentrations are presented in Table 2.

These population-derived parameters were then used to predict the number of patients who would have serum vancomycin concentrations in the reference range using the following regimens: 10 mg/kg/dose every 12-hours, 15 mg/kg/dose every 12-hours, and 20 mg/kg/dose every 12-hours. Table 3 displays the serum vancomycin concentrations calculated for the population and for each of the three subgroups. Both peak and trough serum concentrations were within the reference range in 24 (67%), 10 (28%), and 2 (6%) patients receiving 10, 15, and 20 mg/kg/dose every 12-hours, respectively.

Figures 1–3 describe the relationship between fluid balance and Vd, serum creatinine and the CL of vancomycin, and the total daily dose of furosemide and Vd, respectively. A statistically significant correlation exists between the serum creatinine and the CL of vancomycin (r^2=0.19, P<0.01). As expected, the CL of vancomycin decreased as the patient's renal function worsened (i.e., rising serum creatinine). Additionally, a statistically significant correlation exists between the

Table 3. Predicted Serum Concentrations (µg/mL) Based on Population Pharmacokinetics

	10 mg/kg/dose*		15 mg/kg/dose*		20 mg/kg/dose*	
	P-SVC†	T-SVC‡	P-SVC†	T-SVC‡	P-SVC†	T-SVC‡
Population	27.7±8.2	8.5±3.6	42±2	12.7±5.3	55.4±16.3	17±7.1
Neonate	27.5±9	9.1±4.3	41.3±13.6	13.8±6.5	55±18.1	18.2±8.7
Infant	28.4±8.4	8.2±3.5	42.6±12.6	12.3±5.2	56.7±16.8	16.4±6.9
Child	27±7.1	7.9±2.4	40.5±10.6	11.9±3.6	54.1±14.2	15.9± 4.8

** = dose given q 12-hrs;*
† = peak serum vancomycin concentration;
‡ = trough serum vancomycin concentration

total daily furosemide dose and the Vd for vancomycin (r^2=0.31, P<0.01). As the furosemide dose increased, the Vd for vancomycin decreased proportionally. During the evaluation period, the dose of furosemide that was given intermittently or by continuous infusion was 3.6± 3.1 mg/kg/dose and ranged from 0–15 mg/kg/d. Interestingly, no significant correlation was demonstrated between the patients''fluid balance OR BUN and their Vd (r^2=0.02, P=NS).

DISCUSSION

In most cases, monitoring of vancomycin serum concentrations is unnecessary. However, several exceptions exist, including the administration of concurrent aminoglycosides, patients receiving dialysis, and patients with rapidly changing renal function.[3] Other sources suggest variable vancomycin pharmacokinetics in burn patients,[4,5] neonates,[1] and pediatric patients with cancer.[2] This publication justifies the addition of pediatric cardiology patients to this select group of patients in whom monitoring of serum vancomycin concentration is warranted.

Pharmacokinetics parameters differed from those previously reported for each age group evaluated. For example, Vd normally ranges from 0.47 L/kg for premature neonates to 0.7 L/kg for infants and children.[6] Regardless of the patient's age, our study population had a very small Vd, which was consistent with premature neonates. Additionally, the elimination t1/2 for the population ranged from 5.6 to 6.2 hours. Again, this is consistent with what would be expected in newborns and neonates; however, it is much longer than what would be expected for infants and children.[6]

The correlation between serum creatinine and vancomycin CL has been previously reported.[7,8] However, the association between diuretic dose and Vd has not been. A number of patients in the current report were receiving large doses of furosemide, which appears to reduce the Vd for vancomycin in this population.

There are several possible explanations for the pharmacokinetics parameters noted for this population. One explanation is the correlation between furosemide dose and Vd. This reduction in Vd does not appear to be a direct diuretic effect as evidenced by the lack of correlation between Vd and fluid balance. Another possible explanation for these findings is the influence of cardiac function on the pharmacokinetics of vancomycin. Further research should explore a possible association between ejection fraction and Vd, and CL of vancomycin.

Limitations of this study include the small sample size and the retrospective design. Although vancomycin does display multi-compartment pharmacokinetics, most clinicians and researchers use a one compartment model to describe this agent. This is more practical and makes reported pharmacokinetics information comparable to current clinical practice. Use of a one compartment model has been justified for this type of research in previously published papers.[1,9,10] It is important to acknowledge the potential impact of using a one compartment pharmacokinetic model on our results. If serum concentrations were drawn prior to the end of the distribution phase, a one compartment model would result in an overestimation of ke and CL and an underestimation of Vd. In an attempt to minimize the impact of this effect, all peak serum vancomycin concentrations were collected 1 hour after a 60-minute infusion.

Considering the smaller Vd and longer elimination half-life found for these cardiology patients, a more conservative dosing strategy is warranted. A dose of 10 mg/kg/dose q 12-hours will result in the largest percentage of peak and trough serum vancomycin concentrations within the reference range. Since this population is likely to receive several potential nephrotoxic agents (e.g., loop diuretics, aminoglycosides, cyclosporine) concurrent with vancomycin therapy, monitoring serum vancomycin concentrations, especially trough concentrations, may be prudent. Further investigation of the impact of congenital heart disease on vancomycin pharmacokinetics is warranted.

CONCLUSIONS

Regardless of age, an appropriate empiric dose of vancomycin in all age groups of pediatric cardiology patients is 10 mg/kg/dose every 12-hours. In order to assure adequate CL of vancomycin, routine monitoring of trough serum concentrations is prudent. Special consideration should be given to those with elevated serum creatinine and to those receiving large doses of furosemide.

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