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The Clinical Pharmacology of Vancomycin in Seriously Ill Preterm Infants

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ABSTRACT. The first dose and steady state pharmacokinetics of vancomycin were studied in 16 seriously ill preterm infants (≤34 wk gestational age) with documented *Staphylococcus epidermidis* infections. One infant was dropped from the study due to peripheral flushing occurring during administration of the first dose. Individual vancomycin doses ranged from 9.8 to 17.8 mg/kg and were infused intravenously over 15–37 min. Fifteen infants were studied after the first dose of vancomycin, whereas only 12 of these 15 were able to be studied under steady state conditions. Vancomycin half-life, steady-state volume of distribution, and body clearance averaged 6.0 h, 0.53 liter/kg, and 1.22 ml/min after the first dose and only slight differences were observed in these parameter estimates under steady state conditions. However, substantial accumulation of vancomycin in serum was observed with multiple dosing. Complete 8-h urine collections were possible in 12 of 15 premature infants after the first dose of vancomycin. Overall, 44.6% of the dose was recovered in the urine with a corresponding vancomycin renal Cl_R averaging 0.88 ml/min. Vancomycin body Cl correlated directly with renal Cl_R ($r = 0.88$, $p < 0.001$) and body weight ($r = 0.8$, $p < 0.001$). Vancomycin pharmacokinetic parameter estimates Vdss and Cl correlated directly with body weight, surface area, and postconceptional age. No significant relationships were observed between these parameter estimates and gestational age or postnatal age. Fourteen of 15 infants were treated successfully for their underlying infectious process. These data support the use of lower doses of vancomycin than previously recommended for the treatment of preterm infants. (*Pediatr Res* 22: 360–363, 1987)

Abbreviations

AUC, area under the serum concentration time curve
$t_{1/2}$, half-life
Cl, body clearance
Vdss, steady state volume of distribution
Cl_R, renal clearance
AUMC, area under the moment curve
T, infusion duration

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Nosocomially acquired bacterial infections remain an important cause of morbidity and mortality among infants admitted to neonatal intensive care units (1). The coagulase-negative staphylococci have become increasingly prominent nosocomial pathogens, and are often associated with life-threatening infections (2–4). Battisti *et al.* (5) have reported that *Staphylococcus epidermidis* has replaced the group B streptococci as the pathogen most frequently isolated from blood cultures in neonatal intensive care units. Other investigators and recent reviews have reported similar findings (6, 7).

The increasing incidence of infections caused by β-lactam resistant coagulase-negative staphylococci has necessitated the more frequent use of vancomycin. Despite the drug's widespread clinical use (8), limited data are available describing the clinical pharmacology of vancomycin in newborn infants (9–13). Current vancomycin dosage recommendations for newborn infants are derived primarily from single dose evaluations performed in full-term and older infants (9). More recent multidose studies suggest that lower doses than originally proposed should be used in the treatment of seriously ill preterm infants (11–14). Despite these published evaluations, a paucity of paired first dose steady-state vancomycin pharmacokinetic data in the very low birth weight infant (*i.e.* <1500 g) exists. The purpose of the present study was to describe the first dose and combined steady-state pharmacokinetics of vancomycin in critically ill prematurely born infants with a documented infection due to *S. epidermidis*.

METHODS

Infants ≤38 wk gestational age consecutively admitted to the newborn intensive care unit of Rainbow Babies and Childrens Hospital with a suspected or documented infection caused by *S. epidermidis* were eligible for enrollment into this study. Gestational age was estimated by the maternal menstrual history and by physical examination according to the method of Dubowitz et al. (15). Prior to the initiation of antibiotic therapy, a parental history was obtained, a complete physical examination performed, and blood was obtained for the determination of serum electrolytes, creatinine, urea nitrogen, calcium, phosphorous, alkaline phosphatase, alanine aminotransferase, total and direct bilirubin, total protein, albumin, and complete blood count with differential and platelet count. Urine was sent for urinalysis. Routine clinical laboratory determinations of blood and urine were performed at least twice weekly during the study period. Specimens for bacterial and fungal culture were obtained from available sites including blood, urine, and cerebrospinal fluid. Laboratory determinations were performed by the clinical laboratories of the University Hospitals of Cleveland.

All infants with a presumed infection were begun on an aminoglycoside in combination with a β-lactam antibiotic await-

ing culture results. Infants from whom *S. epidermidis* was isolated from two blood cultures had their initial antibiotic regimen changed to vancomycin and were enrolled. This study was approved by the Institutional Review Board of the University Hospitals of Cleveland and informed, written consent was obtained from a parent or guardian of each infant.

Drug administration and sample collection. Vancomycin (Vancocin, Eli Lilly & Co., Indianapolis, IN) was administered intravenously over 30 min. The vancomycin dose (mg/kg) and dosing interval were selected by each patient's attending physician based on previously published guidelines (7, 8). The first dose and steady state study dose of vancomycin were administered via an auto syringe by a research nurse.

Venous blood samples (≦0.5 ml) for the determination of vancomycin in serum were obtained at 0, 30, 45, 60, 120, 240, 360, and 480 min after the beginning of the infusion and were repeated after the patient had received a minimum of 3 days of uninterrupted therapy. Blood was collected in sterile glass tubes, allowed to clot, and was centrifuged to separate the clot from the serum. Before administration of the first dose of vancomycin, a urine sample was obtained; thereafter, urine was obtained as aliquots from 0–2, 2–4, and 4–8 h after drug administration. Urine sample volumes were measured and recorded and a 1-ml sample was saved. Serum and urine samples were frozen at −70° C until analyzed. All samples were analyzed within 7 days of collection.

Vancomycin concentrations in serum and urine were determined by fluorescence polarization immunoassay (TDX, Abbott Laboratories, North Chicago, IL) (16). The assay limit of detection was 0.5 μg/ml. The between day coefficients of variation were 5.7% at 35 μg/ml vancomycin and 6.8% at 7 μg/ml.

Pharmacokinetic analysis. Model-independent methods were used to describe the biodisposition of vancomycin (17). Serum vancomycin concentrations for each patient were plotted against time on a semilogarithmic scale. AUC was obtained by using the linear trapezoidal rule up to the final measured concentration and extrapolated to infinity following the first dose and to the dosing interval τ, during steady state conditions. The elimination $t_{1/2}$ was determined using the terminal portion of the serum concentration time curve. Vancomycin body Cl was determined using the formula dose/AUC_0^{∞} following the first dose and dose/AUC_0^{τ} during steady state. The Vdss after the first dose was determined using the following equation:

$$\text{Vdss} = \frac{\text{dose} \cdot \text{AUMC}}{\text{AUC}^2} - \frac{\text{dose} \cdot \text{T}}{\text{AUC} \cdot 2}$$

Determination of Vdss at steady state was calculated using the superposition method (18). The Cl_R of vancomycin for each patient was calculated as $Cl_R = A_0^{\infty}/AUC_0^{\infty}$ where A is the cumulative amount of drug excreted (19). Statistical evaluations were performed using the paired and unpaired Student's *t* test and regression analysis.

RESULTS

Demographic and clinical data. A total of 16 seriously ill preterm infants was enrolled into this study. One infant who experienced peripheral flushing ~10 min into the infusion of the first vancomycin dose was withdrawn from the study by his parents. This infant continued on vancomycin therapy without ill effect. The characteristics of the remaining 15 study patients are shown in Table 1. Infants ranged in gestational age from 25–34 wk, post conceptual age from 27–36.5 wk, and postnatal age from 7–43 days. The dose of vancomycin ranged from 9.8 to 17.8 mg/kg per dose; one infant received vancomycin on a q 6 h dosage regimen whereas the remaining 14 infants received the drug q 8 h. All 15 infants were studied after the first vancomycin dose, 12 of these 15 were able to be studied under steady-state conditions.

In addition to prematurity, 12 of the study infants had respiratory distress syndrome as their primary underlying disease; two had necrotizing enterocolitis and one child was born to a drug-addicted mother. All infants had *S. epidermidis* sepsis. Although one infant had a suspected concurrent meningitis, cultures of the cerebrospinal fluid were sterile. All infants had central venous catheters in place, were mechanically ventilated, and continued to receive concurrent aminoglycoside therapy. Serum creatinine concentrations prior to instituting vancomycin therapy ranged from 0.4–1.3 mg/dl. All isolates of *S. epidermidis* were sensitive *in vitro* to ≦4 μg/ml of vancomycin. Fourteen of the 15 infants were treated successfully for their infections with vancomycin. With the exception of the one infant who was withdrawn from the study, no infants experienced any adverse effects that could be directly attributed to vancomycin administration. Although previous investigators have suggested an increased incidence of nephrotoxicity in patients receiving combined aminoglycoside vancomycin therapy (20), we were unable to confirm this finding by repeated serum creatinine determinations and assessment of urine output in our study infants.

Pharmacokinetics. The overall (mean ± SD) vancomycin serum concentration time curve after the first dose and under steady state conditions is shown in Figure 1. End of the infusion peak vancomycin concentrations after the first dose averaged 31.2 μg/ml (range 18.8–62 μg/ml) increasing to 45 μg/ml (range 24.7–73.3 μg/ml) at steady state. Steady state serum vancomycin concentrations obtained 30 min after completion of the drug infusion correlated directly with the dose (mg/kg) administered $r = 0.79$ ($p < 0.005$). Eight-h trough concentrations averaged 9.5 μg/ml (range 5.1–15.3 μg/ml) after the first dose and 19.4 μg/ml (range 8.1–38 μg/ml) at steady state.

First dose and steady state pharmacokinetic parameter estimates for vancomycin are shown in Table 2. Vancomycin elimination $t_{1/2}$, Vdss, and body Cl after the first dose averaged 6 h, 0.53 liter/kg and 1.22 ml/min, respectively. Only slight statisti-

Table 1. *Patient characteristics*

	Mean (±SD)	Range
Male/female 4:11		
Gestational age (wk)	28.4 (2.6)	25–34
Post conceptional age (wk)	31.4 (3)	27–36.5
Postnatal age (day)	20.5 (10.4)	7–43
Body wt (g)	1068.7 (435)	650–2380
Vancomycin dose (mg/kg)	12.6 (2.8)	9.8–17.8
Infusion duration (min)	28.5 (6.6)	15–37

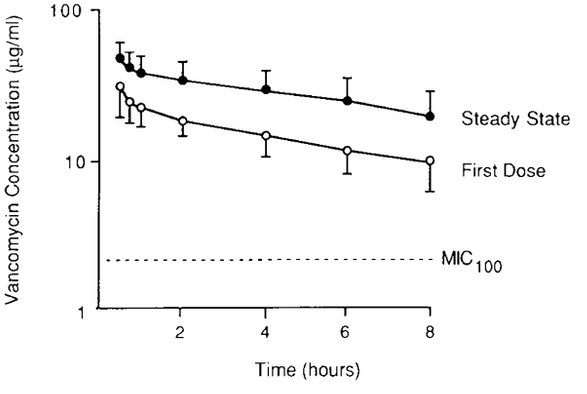

Fig. 1. Overall mean (±SD) vancomycin serum concentration time curve after the first dose (n = 15) and under steady state (n = 12) conditions. All isolates of *S. epidermidis* were sensitive *in vitro* to ≦4 μg/ml vancomycin.

cally insignificant differences were observed in these parameter estimates under steady state conditions. The vancomycin dose administered (in mg/kg) correlated directly with steady state AUC (data not shown $r = 0.75$, $p < 0.005$).

Assessment for relationships that may exist between vancomycin pharmacokinetic parameter estimates and various indices of maturation including gestational age, postconceptual age, postnatal age, body weight, and surface area revealed body weight or surface area as the most significant parameters. Vancomycin Vdss (in liter) correlated directly with patient body weight (in kg) ($r = 0.77$, $p < 0.001$ first dose; $r = 0.89$, $p < 0.001$ steady state) (Fig. 2), and surface area ($r = 0.80$, $p < 0.001$ first dose and $r = 0.89$, $p < 0.001$ steady state). A similar relationship was observed between vancomycin body Cl and patient weight ($r = 0.83$, $p < 0.001$ first dose; $r = 0.89$, $p < 0.001$ steady state) (Fig. 3) and also with surface area ($r = 0.84$, $p < 0.001$ first dose and $r = 0.89$, $p < 0.001$ steady state). No significant relationships were observed between these vancomycin pharmacokinetic parameter estimates and gestational age or postnatal age. A direct but less significant relationship was observed between postconceptual age and vancomycin Vdss ($r = 0.53$, $p < 0.05$ first dose; $r = 0.62$, $p < 0.05$ steady state) and body Cl ($r = 0.56$, $p < 0.05$ first dose; and $r = 0.62$, $p < 0.05$ steady state).

The recovery of vancomycin in the urine after the first dose is shown in Figure 4. Complete timed urine samples were available in 12 of the 15 first dose study patients. Overall, 44.6% of the dose was recovered unchanged in the urine over the 8-h sampling period. The vancomycin Cl_R averaged 0.88 ml/min (Table 2) and correlated directly with vancomycin body Cl ($r = 0.88$, $p < 0.001$) (Fig. 5). Vancomycin Cl_R correlated directly with the infant's body weight ($r = 0.80$, $p < 0.001$), surface area ($r = 0.73$, $p < 0.005$), and postconceptual age ($r = 0.60$, $p < 0.05$), but not with an infant's gestational or postnatal age.

Table 2. *First dose and steady state vancomycin pharmacokinetics in premature infants [mean (±SD)]*

Parameter	First dose ($n = 15$)	Steady state ($n = 12$)
$t_{½}$ (h)	6.0 (2.0)	6.6 (2.1)
Vdss (liter/kg)	0.53 (0.13)	0.52 (0.1)
Cl (ml/min)	1.22 (0.7)	1.16 (0.6)
Cl_R (ml/min)	0.88 (0.8)	
Cpmax (mg/liter)*	31.2 (12)	46.4 (15)
Cpmin (mg/liter)†	9.5 (3.5)	19.4 (9.2)

* 30 min postinfusion.
† 480 min postinfusion.

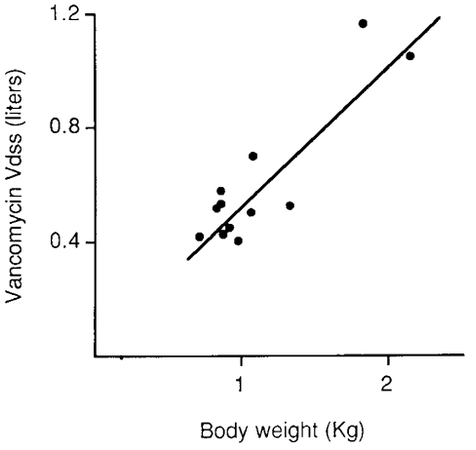

Fig. 2. Relationship between vancomycin Vdss under steady state conditions and body weight ($r = 0.89$, $p < 0.001$).

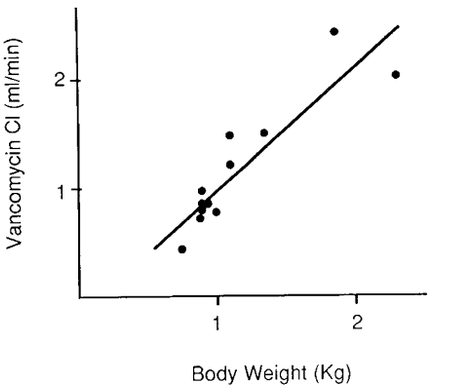

Fig. 3. Relationship between vancomycin body Cl determined at steady state and infant body weight ($r = 0.89$, $p < 0.001$).

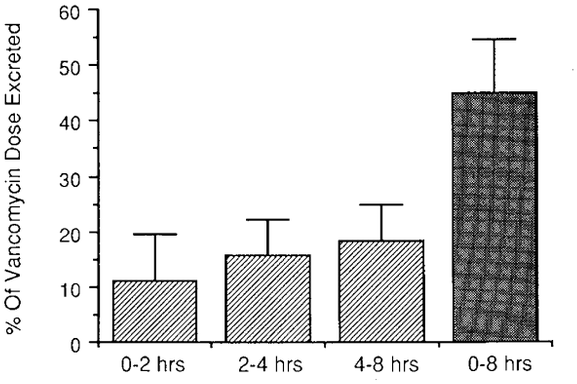

Fig. 4. Urinary recovery of vancomycin after the first dose in 12 premature infants. Each *bar* represents the mean (±SD) for the timed aliquots shown.

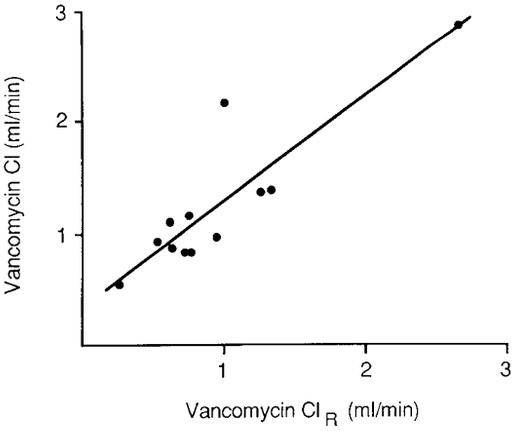

Fig. 5. Relationship between vancomycin body Cl and Cl_R ($r = 0.88$, $p < 0.001$).

DISCUSSION

The biodisposition profile and pharmacokinetics of vancomycin in both pediatric (9–14) and adult patients (21, 22) have been described as complex and characterized by a high degree of individual variation. The vancomycin pharmacokinetic data derived in the present study corroborates these findings, particularly for preterm infants. However, the observed variation in our data was not unexpected considering the drug's dependence upon renal function for body elimination (21, 22) and the ontogeny of human renal function capacity (23, 24) and body water compartmentalization (25).

Previous investigators describing the biodisposition of vancomycin in premature or full term infants and older children have evaluated data derived from either first dose, steady state, or combined first-dose multidose drug administration (9–13). Initial vancomycin dosage recommendations for infants were extrapolated from data derived from mostly single dose determinations (9). These investigators described a direct relationship between vancomycin body Cl and chronological age. However, when these earlier vancomycin dosage recommendations based on an infants chronological age are used, substantial accumulation in serum vancomycin concentrations are observed (Fig. 1). For infants more than 8 days of age, 8-h steady state vancomycin trough concentrations were 2- to 4-fold greater than currently recommended for the treatment of staphylococcal infections (8, 9, 14, 21, 22).

More recent data for vancomycin disposition in premature infants have described highly significant and direct linear relationships between vancomycin body Cl and postconceptional age (12, 13) with limited or no relationship to postnatal age. This finding is most likely related to the observation that postnatal maturation of glomerular filtration rate appears to correlate best with an infant's postconceptional age (23, 24). Naqvi *et al.* (1), Schaible *et al.* (12), and James *et al.* (13) have described direct linear relationships between vancomycin body Cl and postconceptional age with correlation coefficients ranging from $r = 0.649$ to $r = 0.91$. Similar relationships have been observed for other drugs primarily dependent on renal function for body elimination (26, 27). Although in the present study vancomycin body Cl correlated significantly and directly with postconceptional age (steady state Cl, $r = 0.62$, $p < 0.05$), a more significant relationship was observed between Cl and either body weight (steady state, $r = 0.89$, $p < 0.001$) (Fig. 3) or surface area ($r = 0.90$, $p < 0.001$). A similar relationship between vancomycin body Cl and body weight can be identified from the data of Gross *et al.* (10).

This reported variation in the relationship between vancomycin body Cl and either postconceptional age or body weight surface area may be due to the diversity of infant ages at the time of study. Arant (24) in assessing the ontogeny of renal function described both a high degree of interpatient variation and a relative lack of maturation in the functional capacity of the kidney in infants ≦34 wk postconceptional age. These data would suggest that in markedly premature infants, body weight or surface area rather than postconceptional age provided a better reflection of absolute functional renal mass. Additionally, body weight may be a more accurate determinant of maturity than a potentially subjective scoring system.

Over the 8-h study period, 44.6% of the first vancomycin dose was recovered in the urine (Fig. 4). The vancomycin Cl_R averaged 0.88 ml/min and accounted for 88% of the overall body Cl (Fig. 5), reflecting the near complete dependence of vancomycin elimination on renal function. The vancomycin Cl_R correlated directly with body weight ($r = 0.73$, $p < 0.005$) and postconceptional age ($r = 0.54$, $p < 0.05$) but not gestational or postnatal age.

The results of the present investigation support the previous findings of a large degree of variation in vancomycin pharmacokinetic data in premature infants (10–13) and documents the substantial accumulation of serum vancomycin concentrations when drug dose is based upon chronologic age (9). James *et al.* (13) suggest a vancomycin dosing regimen which is graduated based on an infant's postconceptional age or body weight. However, insufficient data are provided to allow a critical evaluation of these recommendations. Using the vancomycin pharmacokinetic parameter estimates derived in the present study to stimulate immediate postinfusion peaks (using a 30-min infusion duration) between 25 and 35 μg/ml, and 12-h trough concentrations between 5 and 10 μg/ml, we recommended a vancomycin dose of 10 mg/kg administered every 12 h in infants ≦36 weeks postconceptional age. Considering the apparent dependence of vancomycin body Cl, Cl_R, and Vdss on body weight (or surface area) and the observed variation in serum vancomycin concentrations, we would recommend the continued pharmacokinetic monitoring of premature infants receiving uninterrupted vancomycin therapy for greater than 3 days.

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