

Vancomycin Pharmacokinetics and Dose Recommendations for Preterm Infants

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The pharmacokinetics of intravenous vancomycin was studied in 20 preterm infants (gestational age, 26.5 weeks \pm 2.6 weeks [standard deviation]; birthweight, 880 \pm 340 g). At the time of the studies their postconceptional age was 36.4 \pm 4.5 weeks. The drug was infused over 30 min in a dose between 9.2 and 18 mg/kg. A highly significant correlation existed between postconceptional age or body weight and vancomycin $t_{1/2}$ and clearance. Serum creatinine concentrations correlated with vancomycin $t_{1/2}$ and clearance. Serum creatinine tended to decrease with increasing postconceptional age. Based on the excellent correlation between age (or weight) and vancomycin pharmacokinetics, dose and dose-interval recommendations are presented.

Vancomycin is often used in the newborn infant to treat coagulase-negative staphylococcal infections, especially with methicillin-resistant strains.

Current recommendations are for steady-state peak concentrations between 30 and 40 mg/liter and a trough less than 10 mg/liter (9). These levels guarantee concentrations above the MIC for staphylococci and below the range associated with nephrotoxicity and autotoxicity. Recommended doses of vancomycin for preterm infants have not yet been established; however, based on current knowledge with other renally excreted drugs (e.g., aminoglycosides) (8), it is conceivable that these infants may need significantly smaller doses due to immature renal function.

In the present study recommendations for vancomycin in preterm infants have been made based on pharmacokinetic analysis.

MATERIALS AND METHODS

Twenty preterm infants in the neonatal intensive care unit at the Hospital for Sick Children, Toronto, participated in the study, which was approved by the Hospital Committee on Human Experimentation. Their gestational age (mean \pm 1 standard deviation [SD]) and birthweight were 26.5 \pm 2.6 weeks (range, 23 to 29 weeks) and 880 \pm 340 g (range, 480 to 1,900 g), respectively. At the time of the study the postconceptual age (mean \pm 1 SD) was 36.4 \pm 4.5 weeks (range, 25 to 41 weeks), and actual weight was 1,300 \pm 570 g (range, 480 to 2,970 g).

Vancomycin was administered for suspected or proven septicemia with resistant *Staphylococcus epidermidis*. The study was conducted after 1 to 7 days of vancomycin therapy (mean, 3.3 \pm 2 days). The drug was infused over 30 min in a dose between 9.2 and 18 mg/kg (mean, 12.8 \pm 2.1 mg) given twice daily.

Serum samples for determination of vancomycin concentrations were drawn just before administration of the dose (trough) and then at three additional time points after the end of the infusion during the same dose interval. Vancomycin

concentrations in serum were determined by the EMIT method (Vancocine; Syva, Palo Alto, Calif.). The coefficient of variation of this test in our laboratory is less than 5% for the entire clinically relevant range. Creatinine concentrations in serum were determined with creatinine analyzers (Beckman Instruments Inc.) at midinterval in 17 infants (6 h after the beginning of infusion of the dose and 6 h before the next dose).

Pharmacokinetic analysis. The concentration-time data were fitted to a one-compartment open model with the NONLIN computer program, with correction for the infusion time and a weighting scheme of $1/C^2$. Correlations between various parameters were studied by least-square regression analysis with the MACFIT program. Both linear and nonlinear (hyperbolic, natural log, and exponential) equations were tested. Equations with the best regression coefficient and the smaller P values are quoted.

Dose recommendations were based on the steady-state equation (8) dose (mg/kg per day) = clearance (liters/kg per day) \times mean concentration (mg/liter) (equation 1), where mean concentration is the midinterval value in steady state. Dose interval τ recommendations were based on the equation (8) $\tau = 1.44 \cdot t_{1/2} \ln C_{\max}/C_{\min}$ (equation 2), where C_{\max} is the peak and C_{\min} the trough concentration. The values of steady-state C_{\max} and C_{\min} were assigned to be 30 and 6 mg/liter, respectively, based on a widely accepted literature recommendation (9) of peak between 25 and 40 mg and trough below 10 mg/liter. Consequently, the mean steady-state concentration was 21 mg/liter (i.e., midinterval level when the peak is 30 mg/liter and the trough is 6 mg/liter). This value is calculated by plotting the assigned steady-state peak (30 mg/liter) and trough (6 mg/liter) concentrations on a semilogarithmic paper and finding the value at the midinterval.

RESULTS

A highly significant negative correlation existed between postconceptional age and vancomycin $t_{1/2}$ ($r = -0.91$, $P < 0.0001$; $y = 2.08 \times 10^7 x^{-3.1}$) (Fig. 1), and there was a positive correlation between postconceptional age and van-

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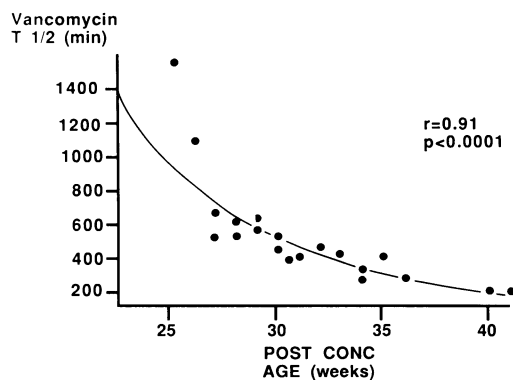


FIG. 1. Correlation between postconceptional age and vancomycin elimination $t_{1/2}$.

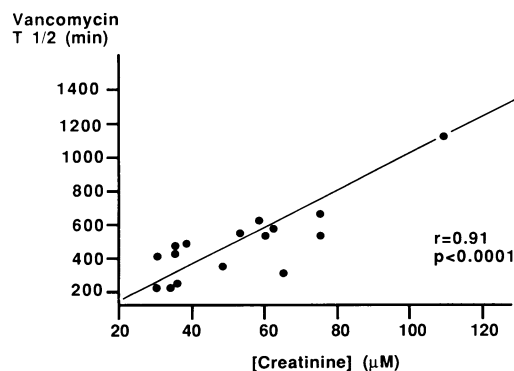


FIG. 3. Correlation between creatinine concentration in serum and vancomycin $t_{1/2}$.

comycin clearance ($r = 0.8$, $P < 0.001$; $y = 0.0014 x^{-1.48}$) (Fig. 2).

Both $t_{1/2}$ ($r = -0.88$, $P < 0.0005$; $y = 4.5 \times 10^5 x^{-0.96}$) and clearance ($r = 0.78$, $P < 0.001$; $y = 0.00018 x^{0.089}$) correlated equally well with body weight. This is well explained by the expected correlation between body weight and postconceptional age ($r = 0.96$, $P < 0.0001$; $y = 133.7x - 2,860$).

The creatinine concentration in serum correlated well with vancomycin $t_{1/2}$ ($r = 0.91$, $P < 0.0001$; $y = 10.7x - 67$) (Fig. 3) and clearance ($r = -0.74$, $P < 0.005$; $y = 2.1 e^{-0.00132x}$) (Fig. 4). Serum creatinine tended to decrease with increasing postconceptional age ($r = -0.62$, $P < 0.01$; $y = 133.7x - 2,860$) (Fig. 5). No correlation could be detected between postconceptional age or weight and distribution volume (V) of vancomycin. Mean V (± 1 SD) was 693 ± 149 ml/kg. Table 1 presents dose and interval recommendations based on body weight or postconceptional age according to equations 1 and 2.

DISCUSSION

In the previous decade it has become apparent that the preterm infant is significantly different from the fullterm infant in handling drugs. For virtually all drugs studied, clearance rates are much slower in the preterm infant, mainly due to immaturity of renal function and hepatic drug metabolism (8). The present study establishes the same pattern with the renally eliminated vancomycin, by confirming a highly significant correlation between postconceptional age or weight and vancomycin clearance rate or $t_{1/2}$. The preterm infant has fewer glomeruli than the full-term

neonate, who in fact has the same number as an adult (1; G. Koren, in G. Koren, C. Prober, and R. Gold, ed., *Antimicrobial Drugs in Infants and Children*, in press). The developmental process of kidney structure and function is associated with prolongation and maturation of the tubules, increase in renal blood flow, and improvement of the filtration coefficient. Improvement of the glomerular filtration rate thus depends on postconceptional age (6).

Our data indicate that vancomycin closely resembles the developmental pattern of gentamicin or amikacin elimination (6). The good correlation between postconceptional age and vancomycin clearance and $t_{1/2}$ permits calculation of optimal dose schedules, because the mean concentration at steady state depends solely on the ratio between dose and clearance (equation 1) and the dose interval depends on $t_{1/2}$, C_{max} , and C_{min} (equation 2).

Most reports on vancomycin-induced nephrotoxicity have been for adult patients (4). However, Dean et al. recently reported vancomycin-associated nephrotoxicity in 11% of the children they studied (3). Serum creatinine levels returned to baseline when the vancomycin peak concentrations were adjusted to 20 to 40 mg/liter and trough concentrations to 5 to 10 mg/liter (3).

Two recent studies have dealt with vancomycin disposition by the preterm infant. Based on only three infants weighing less than 1 kg, Gross et al. concluded that body weight does not influence the clearance rate of vancomycin, and therefore the maintenance dose should not be dependent on weight (5). This conclusion is based on a small sample size. In addition, these investigators did not correct the data for infusion time of the drug. Noqui and colleagues (7) found

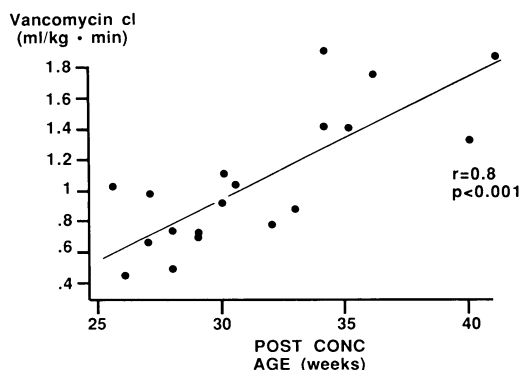


FIG. 2. Correlation between postconceptional age and vancomycin clearance (cl).

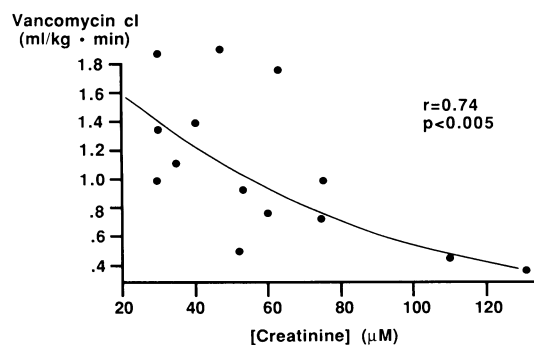


FIG. 4. Correlation between creatinine concentration in serum and vancomycin clearance (cl).

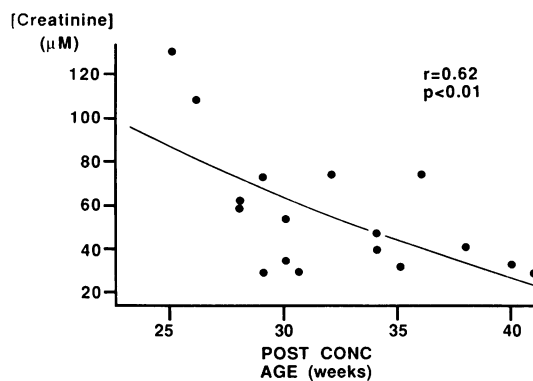


FIG. 5. Inverse correlation between creatinine concentration in serum and postconceptional age.

a gestational age-dependent change in elimination of vancomycin; however, none of their patients were aged less than 32 weeks postconception. Although their data are consistent with the present study, their correlations of age or weight with clearance and $t_{1/2}$ are weak and cannot permit a valid estimation of vancomycin dose schedule.

The gradual age-dependent decrease in serum creatinine (Fig. 5) reflects the improvement in renal function and is consistent with the improvement in vancomycin elimination. However, during the first weeks of life serum creatinine may not be an ideal guide for renal function, as the infant is born with the maternal value of creatinine, and it takes several days or several weeks for excretion of the exogenous creat-

TABLE 1. Recommended doses and dose intervals of vancomycin for preterm infants to maintain a steady-state peak of 30 mg/liter and trough of 6 mg/liter

Postconceptional age (wk)	Body wt		Daily dose (mg/kg)	Dose interval (h)	Dose/injection (mg/kg)
	g	lb			
<27	<800	<1.8	18	36	27
27-30	800-1,200	1.8-2.7	24	24	24
31-36	1,200-2,000	2.7-4.4	36	12-18	18-27
>37	>2,000	>4.4	45	12	22.5

inine and equilibration of creatinine production and secretion (2).

In this study we did not use a loading dose of vancomycin. In general, a loading dose is useful to shorten the time needed to achieve the therapeutic steady-state concentrations. However, the size of the loading dose would not change the concentrations achieved with a certain maintenance dose during steady state, because according to equation 1 in steady state: mean concentration (mg/liter) = [steady-state dose (mg/kg per day)]/[clearance (liters/kg per day)].

The present data clearly indicate that the very low birthweight infant (≤ 1 kg or < 29 weeks postconceptional age) should receive only one-half of the dose given to more mature infants due to a significantly lower clearance rate. As these changes are continuous, we suggest gradual changes in dose schedules (Table 1).

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