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R. Davis Maker
Medical College of Georgia

Joseph T. DiPiro
Virginia Commonwealth University, University of Georgia, jtdipiro@vcu.edu

Jatinder Bhatia
Medical College of Georgia

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Pharmacokinetics of Vancomycin in Critically Ill Infants Undergoing Extracorporeal Membrane Oxygenation

R. DAVIS AMAKER,¹ JOSEPH T. DiPIRO,^{2,3} AND JATINDER BHATIA^{1*}

Departments of Pediatrics¹ and Surgery,² Medical College of Georgia, Augusta, and University of Georgia College of Pharmacy, Athens,³ Georgia

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Extracorporeal membrane oxygenation (ECMO) is a widely used therapy for neonates with respiratory failure. Because of sepsis, many of these infants require antibiotics like vancomycin during ECMO treatment. ECMO transiently alters renal function and increases the circulating blood volume by 75%. Initial vancomycin pharmacokinetics were determined in 12 infants undergoing ECMO to determine an adequate drug administration regimen. Vancomycin dosage was based on current recommendations for weight and gestational age. Pharmacokinetic parameters were determined by fitting the data to a two compartment model. This study yielded a mean steady-state volume of distribution of 1.1 ± 0.5 (range, 0.6 to 2.1) liters/kg and a mean vancomycin clearance of 0.78 ± 0.19 (range, 0.49 to 1.07) ml/min/kg. The mean vancomycin half-life was 16.9 ± 9.5 (range, 8.8 to 42.9) h. Nomogram-calculated creatinine clearance was a significant predictor of vancomycin terminal rate constant and clearance. These data suggest alterations in the pharmacokinetics of vancomycin in infants on ECMO. With the goal of achieving vancomycin concentrations in serum above the MIC for the offending pathogen while using the least amount of the drug necessary, new administration guidelines for term infants without renal impairment undergoing ECMO should be 20 mg of vancomycin per kg at an interval of 24 h. With significant renal impairment, the interval should be extended on the basis of concentrations in serum. In comparison with previously published data, the neonates undergoing ECMO in our study demonstrated a much larger volume of distribution, a lower clearance, and consequently a longer vancomycin half-life.

Extracorporeal membrane oxygenation (ECMO) is a method of cardiopulmonary bypass used to rescue term neonates with respiratory failure (4). ECMO has improved survival from 20 to 80% in a select group of infants with nearly fatal but ultimately reversible pulmonary hypertension (1, 17). Venoarterial ECMO is accomplished by removing blood from the jugular vein, passing it through a membrane oxygenator, and then pumping it back into the aortic arch through the carotid artery. Because ECMO increases the circulating blood volume and transiently alters renal function, it is reasonable to assume that it likewise alters drug pharmacokinetics. In adult cardiopulmonary bypass, it is known that half-life ($t_{1/2}$) is prolonged, clearance (CL) is decreased, and volume of distribution (V) is increased for many drugs (10). These changes have not been demonstrated for vancomycin in children undergoing bypass for cardiopulmonary surgery (8). The few studies that have been done on infants undergoing ECMO defined the pharmacokinetics of gentamicin. Southgate et al. (19) reported an increase in gentamicin $t_{1/2}$ from 5 h in non-ECMO-treated infants to 9.3 h in infants on ECMO. Gentamicin CL was decreased. Gentamicin pharmacokinetics altered by ECMO have been confirmed by other investigators (5, 7). With the emergence of methicillin-resistant staphylococci as an ever-present pathogen, many infants receive vancomycin. This study was designed to determine the pharmacokinetics of vancomycin in infants undergoing ECMO. With these data, revised recommendations for vancomycin administration to ECMO patients were derived.

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MATERIALS AND METHODS

All neonates at the Medical College of Georgia who were undergoing ECMO and had been started on vancomycin for clinical indications were eligible for this study. This study was approved by the Human Assurance Committee at the Medical College of Georgia, and infants were enrolled after informed parental consent was obtained. From January 1994 to March 1995, 12 infants were prospectively enrolled into the study. All 12 of these infants underwent venoarterial ECMO.

The extracorporeal circuit consisted of arterial and venous cannulae (Biomedicus cannulas; Medtronic Biomedicus, Inc., Eden Prairie, Minn.), extracorporeal tubing (Tygon 5-50-HL or Super Tygon 5-65-HL; Norton, Akron, Ohio), a venous reservoir (35-ml capacity R-14 silicone; AVecor Cardiovascular, Inc., Plymouth, Minn.), a membrane oxygenator (Avecor model 0800-2A; AVecor Cardiovascular Inc.), and a heat exchanger (Ecmotherm; AVecor Cardiovascular, Inc.), and the total blood volume was approximately 400 ml.

Vancomycin hydrochloride (Lederle, Inc., Carolina, Puerto Rico) was given at either 15 or 20 mg/kg (intravenously over a 1-h period) at intervals of either 8, 12, or 18 h on the basis of gestational age. Vancomycin was infused for 1 h into the circuit at a point distal to the venous reservoir. Blood samples (0.3 ml) were collected from the venous cannula at a point proximal to the venous reservoir. Samples were drawn over the administration interval after the fourth dose from 11 infants and after the third dose from 1 of the infants because of early decannulation. Drug concentrations were determined immediately before and at 15, 30, 60, and 120 min following completion of the dose infusion. The remaining three concentrations were determined at evenly spaced intervals over the remainder of the administration interval. Drug concentrations in serum were determined by fluorescence polarization immunoassay (TDX System; Abbott Laboratories, Abbott Park, Ill.). The assay is linear from 2 to 100 µg/ml (correlation coefficient, 0.957) with coefficients of variation of <6% at 7.0 µg/ml and <4% at 35 and 75 µg/ml. The lowest measurable level (defined as the concentration which can be distinguished from zero with 95% confidence) was determined to be 2 µg/ml.

Serum creatinine and blood urea nitrogen levels were determined every 12 h during ECMO. Demographic data recorded for each subject consisted of gestational age, birth weight, birth length, and gender. In addition, diagnosis, age when placed on ECMO, hours on ECMO, and outcome were recorded for each infant. Outcome was defined as death or survival. Survival was defined as survival until the time of hospital discharge.

* Corresponding author. Mailing address: Department of Pediatrics, BIW 8078, Medical College of Georgia, Augusta, Georgia 30912. Phone: (706) 721-2331. Fax: (706) 721-7531.

TABLE 1. Patient demographic data

Infant no.	Diagnosis ^a	Birth wt (kg)	Gestational age (wks)	Gender ^b	Age (h) when put on ECMO	Time on ECMO (h)	Serum creatinine (mg/dl)	Outcome ^c
1	PPHN, sepsis	2.84	38	F	12	87	1.0	S
2	PPHN, MAS	3.64	39	F	152	129	0.8	D
3	PPHN, sepsis	3.34	37	M	60	96	1.0	S
4	PPHN, sepsis	2.93	39	M	11	42	1.8	D
5	PPHN, MAS	3.94	41	F	23	221	1.2	S
6	PPHN, sepsis	3.12	38	M	18	69	1.9	D
7	RDS	2.95	38	M	18	66	1.8	S
8	PPHN, sepsis	2.90	39	F	28	91	0.9	S
9	PPHN, MAS	2.73	42	F	54	56	0.7	S
10	RDS	3.58	38	M	41	86	0.6	S
11	PPHN, MAS	3.45	40	M	19	79	1.6	S
12	RDS, sepsis	3.94	39	F	20	88	0.8	S
Mean \pm SD		3.3 \pm 0.43	39 \pm 1.4	6 F, 6 M	38 \pm 39	93 \pm 46	1.18 \pm 0.47	9 S, 3 D

^a PPHN, persistent pulmonary hypertension; MAS, meconium aspiration syndrome; RDS, respiratory distress syndrome.

^b F, female; M, male.

^c S, survival; D, death.

Analysis of data. For each subject, drug concentrations were fitted to a two-compartment, multiple-dose infusion model without weighting (Rstrip; Micro-math, Salt Lake City, Utah). For all models, the model selection criterion (modified Akaike information criterion) was between 2.3 and 6.4 (mean, 4.0). For 11 of 12 subjects, the model selection criterion for the two-compartment model was greater than that for a one-compartment model. No subject had a model selection criterion for a three-compartment model that was greater than that for a one- or two-compartment model. The terminal elimination rate constant (β) was determined from the logarithmic slope of the terminal portion of the drug concentration-versus-time plot. The drug $t_{1/2}$ was determined by the equation $t_{1/2} = 0.693/\beta$. Vancomycin CL was calculated by the equation $CL = \text{dose}/AUC$, where AUC is the area under the serum concentration-time curve for the administration interval at steady state. The AUC was calculated from the sum of intercepts divided by the slopes for the model parameters with AUCs for the last time point to infinity subtracted. V was calculated by the equation $V = \text{dose}/(AUC \cdot \beta)$. By using the pharmacokinetic parameters and a simple one-compartment model, an optimal dose and interval were calculated for each subject to achieve a peak concentration of 30 $\mu\text{g}/\text{ml}$ and a trough of 5 to 10 $\mu\text{g}/\text{ml}$. The drug administration interval was determined from the equation $t'' = [\ln(C_{\text{trough}}/C_{\text{peak}})]/(-\beta)$, where $t'' = \text{interval} - (\text{infusion time} + \text{time from end of infusion until peak})$. The dose was calculated by using a one-compartment monoexponential model by the equation $\text{Dose} = C_{\text{peak}} \times \beta \times V \times (1 - e^{-\beta T})/(1 - e^{-\beta \tau}) \times (e^{-\beta T})$, where τ is the drug administration interval, T is the time after infusion until a peak is drawn, and t is the infusion time. In clinical practice, vancomycin is infused over a 1-h period and the peak concentration is determined 1 h after the end of the infusion. From a clinical standpoint, individual dosage and interval values can be determined from the terminal elimination phase of the concentration-versus-time curve. For this reason, a one-compartment model is appropriate for prediction of the dosage and interval by using β as the elimination rate constant.

Statistical analysis. Creatinine CL was estimated from serum creatinine for each patient by using the Schwartz equation (18). Linear regression analyses (Statgraphics; STSC, Rockville, Md.) were used to test for significant relationships between pharmacokinetic parameters and creatinine CL, gestational age, chronologic age, and birth weight. Multiple regression analysis was used to combine all significant relationships as possible predictors of pharmacokinetic parameters. Standard statistical methods were used to describe demographic data.

RESULTS

Twelve term infants were enrolled in the study, and nine survived. The mean estimated gestational age was 39 weeks, \pm 1.4 (standard deviation) and the mean birth weight was 3.3 \pm 0.4 kg. Half (six) of the infants had documented sepsis. Nine infants had persistent pulmonary hypertension, and three had respiratory distress syndrome. The infants demonstrated a wide range of serum creatinine levels at the time of data collection, from 0.6 to 1.9 mg/dl. Four infants in this cohort had serum creatinine levels of >1.5 mg/dl. Demographic data for the group are presented in Table 1.

Pharmacokinetics. The mean serum drug concentration-ver-

sus-time elimination curve is shown in Fig. 1. The mean pharmacokinetic parameters for the entire group of 12 subjects are as follows: terminal $t_{1/2}$, 16.9 \pm 9.54 (range, 8.8 to 42.9) h; CL, 0.78 \pm 0.19 (range, 0.49 to 1.07) ml/min/kg; V , 1.1 \pm 0.5 (range, 0.6 to 2.1) liters/kg. Data for the entire cohort are shown in Table 2. Minus the four subjects with elevated serum creatinine levels (>1.5 mg/dl), the mean pharmacokinetic parameters for those eight subjects with serum creatinine levels of <1.5 mg/dl are as follows: terminal $t_{1/2}$, 13.2 \pm 4.5 (range, 8.8 to 20.4) h; CL, 0.87 \pm 0.14 (range, 0.64 to 1.07) ml/min/kg; V , 0.99 \pm 0.35 (range, 0.56 to 1.5) liter/kg. Mean pharmacokinetic data of the eight subjects with serum creatinine levels of <1.5 mg/dl are compared to those of the four subjects with serum creatinine levels of >1.5 mg/dl in Table 3. Linear regression analyses of the entire cohort revealed that creatinine CL estimated from serum creatinine levels was a predictor of β ($r^2 =$

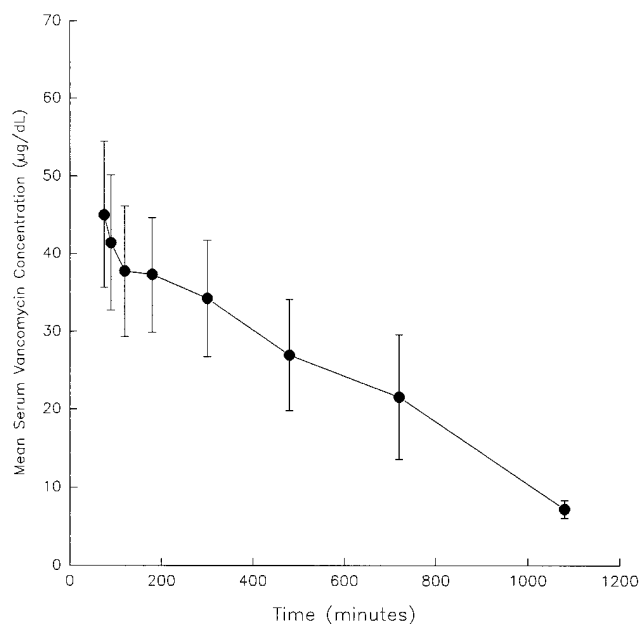


FIG. 1. Mean vancomycin concentration-versus-time data for cohort serum samples. Error bars represent standard deviations.

TABLE 2. Pharmacokinetic data and optimal dose and interval calculated for the 12 infants in this study

Infant no.	$t_{1/2}$ (h)	CL (ml/min/kg)	V (liters/kg)	Optimal dose (mg/kg)	Optimal interval (h)	Serum creatinine (mg/dl)
1	20.4	0.91	1.5	32.5	36	1.0
2	14.7	1.07	1.4	34.1	30	0.8
3	19.3	0.76	1.3	29.8	36	1.0
4	13.1	0.80	0.9	24.9	24	1.8
5	9.5	0.64	0.6	15.1	24	1.2
6	42.9	0.58	2.1	44.1	72	1.9
7	24.8	0.49	1.2	27.6	60	1.8
8	11.4	0.84	0.8	21.1	24	0.9
9	8.8	0.98	0.7	18.7	18	0.7
10	10.8	0.93	0.9	22.5	24	0.6
11	16.4	0.49	0.7	17.4	36	1.6
12	10.9	0.81	0.8	19.8	24	0.8
Mean \pm SD	16.9 \pm 9.5	0.78 \pm 0.19	1.06 \pm 0.45			1.18 \pm 0.45

0.41; $P = 0.023$; correlation coefficient, 0.647) (Fig. 2). Similarly, estimated creatinine CL was a strong predictor of vancomycin CL ($r^2 = 0.71$; $P = 0.003$; correlation coefficient, 0.78) (Fig. 3). Vancomycin CL was positively correlated with chronologic age ($P = 0.04$; correlation coefficient, 0.59). V was inversely related to gestational age ($P = 0.03$; correlation coefficient, -0.61). The relationship between vancomycin $t_{1/2}$ and gestational age did not reach statistical significance ($P = 0.08$; correlation coefficient, -0.51). Multiple regression analysis demonstrated no factors which better predicted pharmacokinetic data than creatinine CL alone.

On the basis of these pharmacokinetic data, the intervals needed to achieve a 1-h postinfusion peak drug concentration of 30 $\mu\text{g/ml}$ and a trough concentration of 5 to 10 $\mu\text{g/ml}$ were calculated. With the interval determined, the dosage per kilogram of body weight was calculated for each subject. The calculated drug administration regimen for each individual is represented in Table 2.

DISCUSSION

Current vancomycin administration recommendations for infants originated from studies which included both premature and term infants (11, 13, 14, 16). Gestational age, postnatal age, and body weight have all been shown to affect the pharmacokinetics of vancomycin. Two studies of vancomycin pharmacokinetics have been done with non-ECMO-treated newborns 40 to 41 weeks in gestational age, a uniform population with a mean gestational age similar to that of a typical ECMO population. Schaad et al. (16) demonstrated a $t_{1/2}$ of 6.7 h, a CL of 1.18 ml/min/kg, and a V of 0.69 liter/kg. Similarly, Naqvi et al. (14) reported a $t_{1/2}$ of 4.87 h, a CL of 1.34 ml/min/kg, and a V of 0.48 liter/kg. These values, therefore, represent usual vancomycin pharmacokinetic parameters for term infants. It should be emphasized that infants undergoing ECMO represent a subgroup of severely ill newborns, and a comparison of

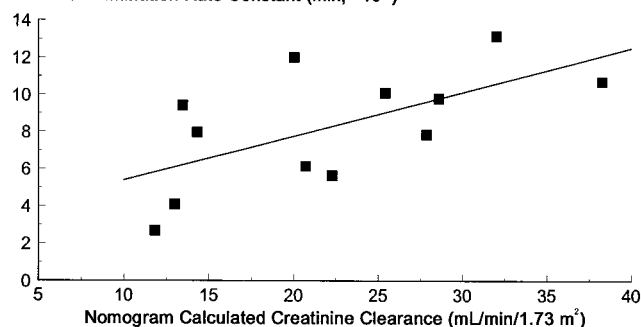
this group to non-ECMO-treated newborns should be made cautiously. Neonates undergoing ECMO in our study demonstrated a much larger V , a lower CL, and consequently a longer $t_{1/2}$ of vancomycin. These alterations of vancomycin pharmacokinetics are consistent with, but much more pronounced than, those previously reported for gentamicin in infants undergoing ECMO (19).

There has been only one prospective investigation of vancomycin pharmacokinetics in neonates undergoing ECMO therapy. Hoie et al. (9) reported the following data for six infants undergoing ECMO: $t_{1/2}$, 7.71 h; CL, 1.10 ml/min/kg; V , 0.68 liter/kg. These data were derived with a one-compartment model from three of the subjects, which could have artificially decreased the $t_{1/2}$ measurements. In addition, no infants with serum creatinine levels of >1.5 mg/dl were included in this study. Nonetheless, $t_{1/2}$ and V were increased, although to a lesser extent than in our study. Reasons for these differences are not clear.

As with adult cardiopulmonary bypass, it is reasonable to assume that ECMO causes a large dilution of plasma, which can result in a larger V for most drugs. For a 4-kg infant, an additional 120 ml of extracellular fluid volume from the ECMO circuit could represent an extracellular fluid volume increase of 10%. In addition, there are large extracellular fluid shifts in any critically ill neonate which could contribute to a variable V at any given time. Immediate increases in extracellular fluid have been demonstrated in neonates undergoing ECMO (2). Often, decreased urine output and/or decreased venous return to the circuit is ameliorated by repeated boluses

TABLE 3. Comparison of vancomycin pharmacokinetic parameters for ECMO-treated patients with serum creatinine levels above and below 1.5 mg/dl

Serum creatinine level (mg/dl)	No. of infants	Mean $t_{1/2}$ (h) \pm SD	Mean CL (ml/min/kg) \pm SD	Mean V (liters/kg) \pm SD
>1.5	4	24.24 \pm 13.39	0.59 \pm 0.15	1.22 \pm 0.63
<1.5	8	13.22 \pm 4.45	0.87 \pm 0.14	0.99 \pm 0.35

Terminal Elimination Rate Constant (min, 10^4)FIG. 2. Vancomycin β versus nomogram-calculated creatinine CL in each subject (correlation coefficient, 0.65; $r^2 = 0.41$; $P = 0.023$).

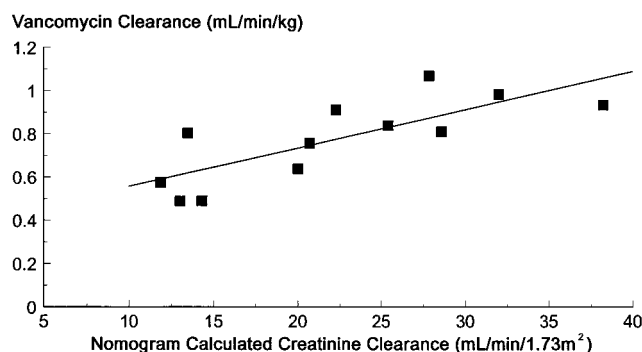


FIG. 3. Vancomycin CL versus nomogram-calculated creatinine CL in each subject (correlation coefficient, 0.78; $r^2 = 0.71$; $P = 0.003$).

of colloid and crystalloid, further causing changes in the volume status.

Vancomycin $t_{1/2}$ is prolonged in premature infants because of a decreased glomerular filtration rate (GFR) (15). Since the GFR increases with gestational age as the kidneys mature (3), there still may be a slight difference between the GFRs of infants with gestational ages of 37 versus 42 weeks. Variations in drug pharmacokinetics can be due in part to subtle differences in GFR as determined by gestational age in a group of term infants. This relationship tended toward statistical significance in our cohort, with $t_{1/2}$ inversely related to gestational age. In addition, renal function in infants on ECMO is often decreased, as evidenced by decreased urine output and transient rise and fall of creatinine (6). These changes are due not only to periods of ischemia and decreased organ perfusion but also to the nonpulsatile blood flow of the ECMO circuit. It has long been known that nonpulsatile flow in dogs causes decreased urine output and sodium excretion, although GFR has not been shown to be directly affected (12). Since vancomycin is cleared primarily by renal excretion, the prolonged $t_{1/2}$ and decreased CL which we have demonstrated most likely reflect renal injury with a decreased GFR, regardless of the mechanism. In this population, we have shown that both $t_{1/2}$ and drug CL are strongly correlated with estimated creatinine CL, as expected.

Individual dosages and intervals must therefore be arrived at by careful consideration of renal function. Previously, Hoie et al. (9) had recommended a vancomycin dose of 20 mg/kg at an 18-h interval for infants on ECMO with serum creatinine levels of <1.5 mg/dl. Our data indicate that infants on ECMO with serum creatinine levels of <1.5 mg/dl should be given vancomycin no more frequently than every 24 h. In two of these eight infants, even a 24-h interval would have produced trough concentrations of 13.5 and 14 μ g/ml, respectively. The ideal dosage for this population is between 20 and 25 mg/kg. For the four infants with serum creatinine levels of >1.5 mg/dl, the proper intervals ranged from 24 to 72 h and the ideal dosage remained roughly the same. On the basis of these data, we recommend an initial dose of 20 mg/kg and an administration interval of 24 h for infants on ECMO without significant renal impairment. For infants on ECMO with significant renal impairment (serum creatinine levels of >1.5 mg/dl) who require vancomycin therapy, we recommend an initial one-time dose of 20 mg/kg. Drug concentrations in serum should then be determined at 12 and 24 h after the one-time dose so that an

individual administration regimen can be derived for each patient. A patient with renal failure could then be given another dose when the concentration is calculated to fall below 10 μ g/ml of serum.

In summary, ECMO appears to alter vancomycin pharmacokinetics by decreasing drug CL and therefore prolonging the $t_{1/2}$ by up to 100% compared with published reports on non-ECMO-treated infants. V is increased 50% above that of non-ECMO-treated infants. Estimated creatinine CL is strongly correlated with both drug CL and β and can be used to predict the appropriate vancomycin dosage and interval.

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