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Pharmacokinetics of Gentamicin in Neonates on Extracorporeal Membrane Oxygenation

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Extracorporeal membrane oxygenation (ECMO) has been used in more than 1,000 infants in 50 centers in the United States. The extracorporeal circuit contains approximately 400 ml of blood, an amount exceeding the blood volume of most full-term neonates. The effect of this additional blood volume on drug disposition is unknown. In this study, we determined the pharmacokinetic parameters of gentamicin in 10 infants on ECMO. Gentamicin concentrations were determined by a fluorescence polarization immunoassay. Pharmacokinetic parameters were determined from these concentrations by using a two-compartment model. Our study demonstrated a mean steady-state volume of distribution of 0.51 ± 0.11 liters/kg, a figure similar to that in previous studies of full-term infants. The elimination half-life was found to be prolonged (mean, 573 ± 263 min). The creatinine level in the plasma of the infants was found to be a statistically significant predictor of elimination half-life. Recommendations regarding initial dosing levels of gentamicin in infants on ECMO are made.

Extracorporeal membrane oxygenation (ECMO) is a process involving prolonged partial cardiopulmonary bypass which is used to support life in infants dying of reversible cardiopulmonary disease. The technique has been used in more than 1,000 infants in 50 centers in the United States, with approximately 80% surviving (2). During ECMO, blood is drained from the right atrium, pumped through a silicon membrane oxygenator, rewarmed, and then returned to the aortic arch of the infant. The extracorporeal circuit contains approximately 400 ml of blood, an amount exceeding the blood volume of most full-term neonates (9). The effect of this additional volume on drug disposition (distribution and elimination) is not known. If drug disposition is substantially altered in infants on ECMO, standard drug dosages and dosing intervals may not be appropriate in these infants.

The purposes of this study were to determine the pharmacokinetics of gentamicin in infants on ECMO and to formulate an approach to gentamicin dosing regimens for this group of babies.

MATERIALS AND METHODS

Infants were eligible for the study if they were started on ECMO within the prior week at the Medical College of Georgia and were receiving gentamicin. Ten infants were prospectively included in the study. Two ECMO patients were not included during the study period, owing to parental refusal of consent in one case and nonavailability of the investigators in another. The study was approved by the Medical College of Georgia Human Assurance Committee, and informed consent was obtained from a parent in each case.

The extracorporeal circuit consisted of arterial and venous cannulae (Argyle Chest Tubes; Sherwood Medical, St. Louis, Mo.), extracorporeal tubing (Tygon Hancock Extracorporeal, Inc., King of Prussia, Pa.), a venous blood reservoir (50-ml capacity; SciMed Life Systems, Minneapolis, Minn.), a membrane lung (Kolobow, model 0800-2A; SciMed), and a heat exchanger (Omnitherm, model D-17-14; SciMed), with a total blood volume of about 400 ml.

Gentamicin sulfate (10 mg/ml; Elkins-Sinn, Inc., Cherry Hill, N.J.) was administered to all the infants soon after birth in a dose of approximately 2.5 mg/kg based on birthweight. Owing to weight increases seen in most of these infants after birth, the actual weight-based doses studied ranged from 2.04 to 2.42 mg/kg. The doses of gentamicin were administered over a 1-min infusion into the extracorporeal circuit via a port distal to the venous-blood reservoir. The doses were administered every 12 h in nine infants and every 18 h in one infant.

Blood samples (2 ml each) were drawn from the extracorporeal circuit via a port proximal to the venous-blood reservoir immediately before and 2, 15, 45, 120, 240, 480, and 720 min after a dose of gentamicin was given. The samples were collected during one dosing interval after the third to ninth gentamicin doses. The samples were centrifuged, and the plasma was separated and frozen at −80°C until analysis.

Gentamicin concentrations were determined by a fluorescence polarization immunoassay (TDX System; Abbott Laboratories, Dallas, Tex.). The interday coefficient of variation for this test over the range of values determined averaged 4.8%.

Creatinine levels in serum and blood urea nitrogen levels were determined for each infant during the study period. Urine output was estimated for each infant from diaper weights.

Data analysis. For each individual, the gentamicin concentrations were fitted to a two-compartment model, assuming elimination from the central compartment only, by using a program for multiple-dose bolus injections (PCNONLIN; Statistical Consultants, Inc., Lexington, Ky.). The pharmacokinetic parameters clearance (CL), volume of distribution at steady state (V_{ss}), and terminal elimination half-life ($t_{1/2\beta}$) were determined as follows: CL = dose/area under plasma concentration-time curve (AUC), where AUC = $A/\alpha + B/\beta$ and A, B, α, and β are the intercepts and exponents

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TABLE 1. Patient characteristics

Infant	Diagnosis[a]	Birth wt (kg)	Study wt (kg)	Gestational age (wk)	Creatinine level in serum (mg/dl)	BUN[b] (mg/dl)	Urine output (ml/kg per h)
1	MAS	4.10	4.85	43	1.4	27	4.1
2	MAS/PFC	3.47	3.50	41	1.2	12	4.5
3	HMD	2.81	3.23	36	1.6	23	4.1
4	MAS	3.50	3.80	40	1.3	17	6.0
5	MAS/PFC	3.00	3.40	42	1.6	14	1.8
6	DH	2.69	2.69	38	1.1	11	4.2
7	MAS	4.30	4.27	41	0.8	17	2.8
8	MAS/PFC	3.20	3.87	40	2.5	23	1.9
9	PFC	3.19	3.58	Term	0.5	28	2.7
10	DH	2.54	2.94	40	1.3	13	1.5

[a] Abbreviations: MAS, meconium aspiration syndrome; PFC, persistent fetal circulation; HMD, hyaline membrane disease; DH, diaphragmatic hernia.
[b] BUN, Blood urea nitrogen.

determined from the model, and $V_{ss} = [(A/\alpha^2 + B/\beta^2) \times \text{dose}]/\text{AUC}^2$. Alpha and beta half-lives were determined from the slopes of the initial and terminal portions of the curve of the logarithm of the drug concentration versus time by $t_{1/2\alpha} = 0.693/\alpha$ and $t_{1/2\beta} = 0.693/\beta$, respectively.

From the calculated pharmacokinetic parameters, an optimal dosage was recalculated for each individual based on the known V_{ss} and β. The dosage was calculated to achieve steady-state concentrations in plasma of 6 μg/ml 15 min after intravenous injection (peak) and to achieve a trough of 1.5 μg/ml immediately before the next dose. The dosage was determined by a one-compartment open model to predict steady-state dosage as follows:

$$\text{Dose} = [C_{peak} \times \beta \times V_{ss} \times (1 - e^{-\beta\lambda})]/e^{-\beta(0.25)}$$

where λ = dosing interval, which is adjusted so that $C_{trough} \approx 1.5$ μg/ml.

In vitro studies. To determine whether the ECMO circuit itself might sequester gentamicin, we injected a 3.0-mg dose of gentamicin into an isolated circuit containing 370 ml of blood. No decline in gentamicin levels was observed during the 8-h sampling period.

Statistical analysis. Stepwise regression analysis of creatinine blood urea nitrogen levels in plasma, gestational age, and urine output as possible predictors of the elimination half-life was performed.

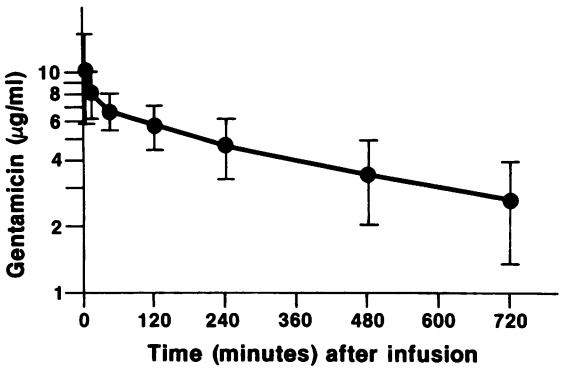

FIG. 1. Gentamicin concentration versus time. Each point represents the mean concentration for 10 infants. The error bars represent 1 standard deviation.

RESULTS

Nine of the ten infants studied survived. Selected characteristics of the infants are presented in Table 1. Seven of the infants had persistent fetal circulation and/or meconium aspiration syndrome, two had a diaphragmatic hernia, and one had hyaline membrane disease.

The estimated gestational age of the infants was between 36 and 43 weeks (as determined by the referring hospitals in most cases), with infant no. 9 being characterized only as "term." The creatinine levels in serum ranged from 0.5 to 2.4 mg/dl, the blood urea nitrogen levels in serum were between 11 and 28 mg/dl, and the urine output ranged from a low of 1.5 ml/kg per h to a high of 6.0 ml/kg per h.

Pharmacokinetics. The mean drug concentration versus time curve for the 10 infants is illustrated in Fig. 1. The mean concentrations of gentamicin in serum 45 min and 12 h after infusion were 6.7 ± 1.25 and 2.60 ± 1.26 μg/ml, respectively.

The gentamicin pharmacokinetic parameters for each infant are provided in Table 2. The mean parameters were as follows: AUC, 3,300 ± 1,095 μg · min/ml (range, 1,554 to 4,790 μg · min/ml); V_{ss}, 0.51 ± 0.11 liters/kg (range, 0.36 to 0.71 liters/kg); CL, 2.78 ± 1.55 ml/min (range, 1.46 to 6.08 ml/min); and $t_{1/2\beta}$, 573 ± 263 min (range, 191 to 950 min). The $t_{1/2\alpha}$ ranged from 0.41 to 4.0 min (mean, 12.6 ± 13.0 min). Linear regression analysis revealed the creatinine level in serum to be a strong predictor of the gentamicin elimination half-life ($r^2 = 0.668$, $P < 0.01$). No influence of blood urea nitrogen levels in serum, urine output, or gestational age on half-life was found. Patient no. 9 was not included in these analyses owing to the absence of a numerical gestational age in the record.

TABLE 2. Pharmacokinetic parameters for gentamicin in patients on ECMO

Infant	AUC (μg · min/ml)	$t_{1/2\beta}$ (min)	CL (ml/min)	V_{ss} (liters/kg)	Optimal dose	
					Dose (mg/kg)	τ (h)
1	3,759	479	2.66	0.36	1.7	16
2	3,434	729	2.47	0.71	3.3	24
3	4,790	910	1.46	0.57	2.7	30
4	3,562	454	2.53	0.43	2.1	16
5	4,172	788	1.80	0.60	2.6	24
6	2,817	494	1.95	0.50	2.3	16
7	1,645	191	6.08	0.37	2.0	8
8	4,502	950	1.78	0.62	2.8	30
9	1,554	234	5.15	0.47	2.3	8
10	3,066	498	1.96	0.47	2.2	16

DISCUSSION

Previous studies of full-term infants have demonstrated a volume of distribution for gentamicin ranging from 0.5 to 0.6 liters/kg (3, 7, 10, 11). The values were similar in the infants in our study, despite the additional approximately 400 ml of circulating blood volume. The distribution of gentamicin beyond the vascular space has apparently minimized the effect of the additional blood volume.

The elimination half-life of gentamicin in newborns has a wide range of reported values, with several studies demonstrating an inverse relationship between gestational age and half-life (1, 4). This relationship is usually explained as an effect of the decreased glomerular filtration rate in infants of less than 34 weeks postconceptive age (6). All of the infants in our study had a gestational age of 35 weeks or more. A relatively narrow range for gentamicin half-life (4.5 to 6.0 h) is seen in the full-term neonate (4, 8, 11). The mean half-life seen in our study (573 min) is unusually long. Since gentamicin is cleared almost entirely by the kidneys (5), the prolonged half-life may reflect renal injury with a reduced glomerular filtration rate in this group of extremely ill infants. We found creatinine concentrations in plasma to be strongly correlated with the elimination half-life. Thomson et al. (10) likewise found creatinine levels in plasma to be a significant determinant of gentamicin disposition. Another factor which one might consider for our group of infants is the response of the kidneys exposed to nonpulsatile blood flow. Under experimental conditions, nonpulsatile perfusion of the kidneys of dogs results in diminished urine production and sodium excretion (5). Glomerular filtration rate, however, is unaffected.

On the basis of our results, we can make recommendations regarding gentamicin dosing in infants on ECMO. By using the methods described above, we determined the retrospective ideal dosing regimens for each of our 10 patients (Table 2). For the group, the mean ideal dose was 2.4 ± 0.5 mg/kg (range, 1.7 to 2.8 mg/kg) and the mean ideal dosing interval was 18.8 ± 8 h (range, 8 to 30 h). When prescribing gentamicin for an infant on ECMO, therefore, a dose of 2.5 mg/kg would be a reasonable starting point. The appropriate dosing interval is more variable and will have to be determined individually by monitoring concentrations in serum over time. Finally, further dosage adjustments may be necessary when ECMO is completed if gentamicin administration is continued. The extent of these adjustments cannot be predicted by the present study.

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