Gentamicin Pharmacokinetics in Term Neonates Receiving Extracorporeal Membrane Oxygenation

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Extracorporeal membrane oxygenation (ECMO) may affect the pharmacokinetics of certain drugs. The objectives of this study were to determine (1) the pharmacokinetics of gentamicin in neonates on ECMO and compare them to reported values for a similar patient population not on ECMO, (2) if the pharmacokinetics of gentamicin differ between venous-venous and venous-arterial bypass, and (3) if the pharmacokinetics of gentamicin are affected by oxygenator surface area (0.6 m^2 vs 0.8 m^2 oxygenators). The medical records of 29 term neonates who received gentamicin while on ECMO were reviewed. Data collected included gentamicin dosage, peak and trough serum concentrations determined at steady state, duration of treatment, time on ECMO, daily weights, and pertinent laboratory values. An initial dosage of gentamicin 2.5 mg/kg every 18 hours is suggested for term neonates on ECMO. Dosage adjustments should be based on gentamicin serum concentrations, and modifications may also be required after ECMO.
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Extracorporeal membrane oxygenation (ECMO) involves the use of prolonged cardiopulmonary bypass in neonates with severe respiratory failure. This allows for a period of lung rest and recovery without the potentially damaging complications associated with prolonged mechanical ventilation, and is considered life saving for infants at high risk of dying from respiratory failure (Figure 1).[1] Since the technique was pioneered in the mid-1970s, more than 4000 infants have received ECMO for respiratory failure. At present, approximately 1000 patients are being added to the National Registry in Ann Arbor, Michigan, each year.[2]

Several ECMO-related factors can theoretically affect the pharmacokinetics of certain drugs. The ECMO circuit presents a large surface area for adsorption of drugs onto a foreign surface, theoretically increasing the volume of drug distribution and reducing the bioavailability of the first dose. Three different sizes of membrane oxygenators are used in newborns (0.4, 0.6, 0.8 m^2); the one used is primarily dependent on the size of the specific patient. The ECMO circuit is primed with approximately 400 ml blood, which exceeds the blood volume of most full-term neonates[3] and may increase the volume of distribution of a drug.

The ECMO circuit is most commonly introduced by venoarterial (V-A) bypass. In this technique oxygenated blood is delivered to the aorta through combined output of the mechanical pump and left ventricle. Total delivery is fixed by preload; however, at high pump flow rates, left ventricle output is minimal and nonpulsatile blood flow can result. Kidney function can be altered by changes in renal blood flow patterns. Nonpulsatile flow decreases urine output and sodium excretion in the absence of significant changes in mean arterial pressure, renal blood flow, or glomerular filtration rate.[4] This flow pattern could potentially affect drugs that are eliminated primarily by the renal route.

Patients on ECMO often have drastic changes in total body water,[5] presumably extracellular water, which may also increase the volume of distribution of a drug. The fluid overload that occurs during ECMO may require the use of hemofiltration in some infants. In addition to water, the hemofilter is

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Table 1. Pharmacokinetic Data for Patients on V-A Bypass

Diagnosis	Oxygenator (m^2)	Pharmacokinetic Values K_{el} (hr^{-1})	Half-life (hrs)	V_d (L/kg)	TBC (L/hr)
PPHN, RDS	0.8	0.08	8.7	0.81	0.249
MA, RDS	0.6	0.05	13.9	0.78	0.121
Fetal distress	0.6	0.07	9.8	0.73	0.156
MA, Ebstein anomaly	0.8	0.05	13.9	0.66	0.121
MA, RDS, PPHN	0.8	0.11	6.3	0.39	0.129
RDS, congenital anomaly	0.8	0.07	9.9	0.47	0.125
DH, RDS	0.8	0.06	11.6	0.59	0.122
DH, RDS	0.8	0.08	8.7	0.66	0.195
MA, RDS	0.6	0.07	9.9	0.73	0.166
DH	0.8	0.06	11.6	0.74	0.169
Sepsis	0.6	0.08	8.7	0.48	0.193
RDS, sepsis	0.6	0.06	11.6	0.74	0.117
RDS, DH	0.8	0.08	8.7	0.48	0.115
RDS, MA, sepsis	0.8	0.12	5.8	0.46	0.249
R/O sepsis	0.8	0.05	13.9	0.70	0.171
DH, R/O sepsis	0.8	0.09	7.7	0.37	0.110
Mean		0.074	10.04	0.61	0.157
±SD		0.02	2.45	0.15	0.046

PPHN = persistent pulmonary hypertension of the newborn; RDS = respiratory distress syndrome; MA = meconium aspiration; DH = diaphragmatic hernia; R/O = rule out.

capable of removing most drugs with molecular weights less than 5200 daltons,[6] and therefore could increase drug clearance.

Gentamicin, a commonly used antibiotic for the treatment of neonatal sepsis, is an example of a drug whose volume of distribution and clearance could be significantly changed by any or all of these factors. Therefore, the objectives of this retrospective study were to determine the elimination rate constant (K_{el}), volume of distribution (V_d), total body clearance (TBC), and elimination half-life of gentamicin in newborn infants receiving ECMO and compare these values to a non-ECMO population of comparable gestational age; to identify the potential differences in the drug's pharmacokinetics between groups receiving ECMO by V-A and venovenous (V-V) bypass; and to identify potential differences in the pharmacokinetics of gentamicin in patients on oxygenators measuring 0.6 m^2 versus 0.8 m^2, which are most commonly used in our nursery.

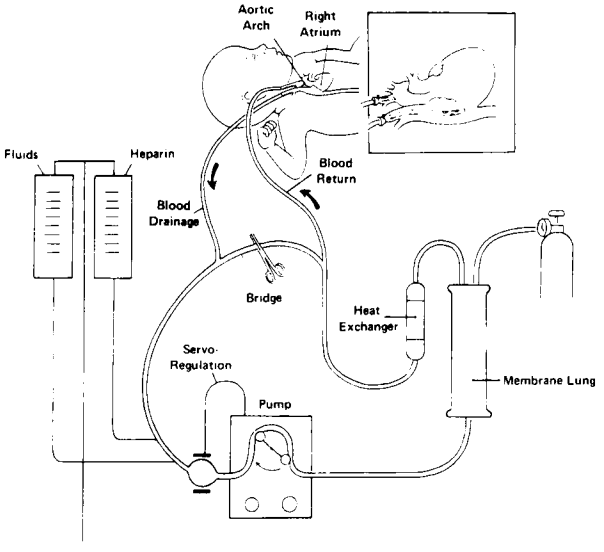

Figure 1. Schematic diagram of the extracorporeal membrane oxygenation circuit.

Methods

The most frequently used ECMO circuit consisted of arterial and venous cannulas, extracorporeal tubing, venous reservoir, membrane oxygenator (SciMed; SciMed Life Systems, Inc., Minneapolis, MN), and heat exchanger (Ecmotherm; SciMed Life Systems, Inc.). If a hemofilter was required in the circuit, it was either a Minifilter or Minifilter Plus (W.R. Grace,.Danvers, MA).

Data Collection

Medical records of all neonates who received V-V or V-A ECMO between July 1988 and December 1989 were reviewed. Based on detecting a 20% difference in gentamicin pharmacokinetics between these patients and the values reported in the literature for full-term neonates, a minimum sample of 26 patients was

Table 2. Pharmacokinetic Data for Patients on V-V Bypass

Diagnosis	Oxygenator (m^2)	Pharmacokinetic Values K_{el} (hr^{-1})	Half-life (hrs)	V_d L/kg	TBC (L/hr)
RDS pneumonia	0.8	0.09	7.7	0.69	0.210
PFC, MA, pneumonia	0.8	0.06	11.4	0.80	0.180
PFC, RDS, TTN	0.8	0.07	9.9	0.52	0.162
PFC, MA, RDS	0.6	0.11	6.3	1.10	0.370
MA	0.8	0.07	9.9	0.97	0.290
PPHN, MA	0.8	0.10	6.9	0.71	0.254
RDS, R/O sepsis	0.8	0.07	10.0	0.94	0.239
DH, RDS	0.8	0.04	17.3	0.63	0.083
RDS, R/O sepsis	0.8	0.04	17.3	0.45	0.063
RDS, R/O sepsis	0.8	0.05	13.9	0.44	0.095
RDS, sepsis	0.8	0.07	9.9	0.60	0.225
MA, ?RDS	0.6	0.09	7.7	0.57	0.189
Sepsis, pneumonia	0.8	0.06	11.6	1.17	0.229
Mean		0.071	10.75	0.74	0.199
± SD		0.022	3.43	0.23	0.086

RDS = respiratory distress syndrome; PFC = persistent fetal circulation; MA = meconium aspiration; PPHN = persistent pulmonary hypertension of the newborn; DH = diaphragmatic hernia; TTN = transient tachypnea of the newborn; R/O = rule out.

determined to be required.[7-11] A total of 68 patients receiving ECMO were reviewed, of whom 29 were included in the final data analysis. The others were not included due to uncertainty of blood sampling times in relation to dose or steady-state conditions, or their being preterm (<36 wks gestational age).

The information collected from the medical records included patient demographics; diagnosis; gentamicin dosage; sampling times for peak and trough concentrations; duration of treatment with gentamicin; total time spent on ECMO; results of renal function tests including urine output, blood urea nitrogen, and serum creatinine; and daily weights during gentamicin therapy. Gentamicin serum samples were considered appropriate based on charting times if blood for the trough concentrations was obtained 0–15 minutes before the start of the next infusion and for the peak concentrations 30 minutes after a 30-minute infusion. All serum concentrations were measured after a minimum of four doses on a 12-hour dosing interval.

Gentamicin was administered over 30 minutes into the ECMO circuit using a syringe pump. The site of administration was generally a port proximal to the venous blood reservoir. The gentamicin dosage for all infants included in the study was 2.5 mg/kg based on birth weight, given every 12 hours initially. If required, dosage adjustments were made based on the first set of serum concentrations measured at steady state on ECMO. Repeat concentrations were generally not obtained. The concentrations were determined by TDx fluorescent polarization immunoassay (Abbott Laboratories, Abbott Park, IL). The interday coefficient of variation for this assay over the range of concentrations determined in the study was less than 5%.

Data Analysis

The pharmacokinetics of gentamicin were calculated using the following standard equations:

$$K_{el} = \ln C_1 - \ln C_2 / t_2 - t_1$$

$$t_{1/2} = 0.693 / K_{el}$$

$$TBC = \frac{\frac{(dose/t_{inf})}{C_{pss}} \cdot (1 - e^{-K_{el} \cdot t_{inf}})}{1 - e^{-K_{el} \cdot \tau}} \cdot (e^{-k_{el} \cdot t_2})$$

$$V_d = TBC/K_{el}$$

where K_{el} is the elimination rate constant, $t_{1/2}$ is the half-life, V_d is the volume of distribution, TBC is the total body clearance of gentamicin, C_{pss} is the steady-state gentamicin peak concentration, t_{inf} is the time of infusion, τ is the dosing interval, and t_2 is the time from the end of infusion to when the peak was drawn.

The data were stratified to group patients by type of bypass, V-A or V-V, and by size of oxygenator, 0.6 or 0.8 m^2. The mean pharmacokinetics of gentamicin in each group were then compared using Student's *t* test. A p value of less than 0.05 was required for significance. Since only two point serum concentration-time data were available, it was not possible to evaluate the data using compartmental modeling methods.

Table 3. Comparison (mean ± SD) of Gentamicin Pharmacokinetics in Patients on V-A vs V-V Bypass and on 0.6 m^2 vs 0.8 m^2 Oxygenator

	No. of Pts	K_{el} (hr^{-1})	Half-life (hrs)	V_d (L/kg)	TBC (L/hr)
Bypass Type					
V-A	16	0.074 ± 0.02	10.04 ± 2.45	0.61 ± 0.15	0.157 ± 0.046
V-V	13	0.071 ± 0.02	10.75 ± 3.43	0.74 ± 0.23	0.199 ± 0.086
p value		> 0.05	>0.05	>0.05	>0.05
Oxygenator					
0.6 m^2	7	0.076 ± 0.02	9.70 ± 2.51	0.730 ± 0.195	0.187 ± 0.086
0.8 m^2	22	0.071 ± 0.02	10.57 ± 3.17	0.648 ± 0.2	0.172 ± 0.064
p value		>0.05	>0.05	>0.05	>0.05

Results

The primary diagnosis of the 29 infants in the study included one or more of following: meconium aspiration syndrome, pneumonia, diaphragmatic hernia, sepsis, and respiratory distress syndrome. Mean (±SD) gestational age and birth weight were 39.2 ± 2.7 weeks and 3.35 ± 0.71 kg, respectively. Serum creatinine concentrations ranged from 0.3–2.4 mg/dl and blood urea nitrogen from 5–66 mg/dl. Urine output during the course of gentamicin therapy ranged from 0–7.9 ml/kg/hour. Pharmacokinetic data as well as information on type of bypass and oxygenator size are shown in Tables 1 and 2.

The calculated pharmacokinetics (mean ± SD) for all 29 patients were as follows: k_{el} 0.072 ± 0.02 $hour^{-1}$, half-life 10.36 ± 2.95 hours, V_d 0.668 ± 0.2 L/kg, and TBC 0.05 ± 0.02 L/kg/hour. The calculated dosing interval based on these values, and to obtain a desired peak gentamicin concentration of 6 mg/L with a dose of 2.5 mg/kg, was 14.55 hours.

Statistical analysis of gentamicin pharmacokinetics for V-A versus V-V bypass and 0.6- versus 0.8-m^2 oxygenators did not yield any significant differences ($p > 0.05$) (Table 3).

Discussion

Gentamicin is commonly used for the treatment of neonatal sepsis, and its pharmacokinetics can be significantly altered during ECMO. We determined its pharmacokinetic values in 29 infants of greater than 36 weeks gestational age receiving ECMO using two different bypass techniques and two different sizes of oxygenators. Although retrospective, our study has the advantage of larger sample size than other reports in the literature that evaluated gentamicin pharmacokinetics in term newborn infants. The drug's volume of distribution in a population of neonates not on ECMO ranged from 0.5–0.6 L/kg[7,8] The mean V_d in our study population was similar—0.66 ± 0.2 L/kg. In addition, a 30% increase in membrane surface area (0.6–0.8 m^2) did not affect V_d, suggesting no apparent drug adsorption onto the oxygenator membrane. Our data are consistent with another report in which no change in serum gentamicin concentration was observed during an 8-hour sampling period after the administration of a 3-mg dose into the ECMO circuit, indicating that no substantial sequestration occurred.[12] We are confident comparing those findings to our results since the type of oxygenator used in both studies was the same.

That group also reported a steady-state V_d and elimination half-life of 0.51 ± 0.11 L/kg and 9.55 ± 4.38 hours, respectively, whereas other investigators reported values of 0.78 L/kg and 8.7 hours, respectively.[13] In a group of 18 neonates the elimination half-life, V_d, and TBC were 10 hours, 0.58 L/kg, and 0.042 L/kg/hour, respectively.[14] Our V_d was midway between these reported values. The elimination half-life of gentamicin in term newborns ranges from 5–6 hours, although substantial interindividual variations have been reported.[9–11] The mean half-life in our study population was 10.3 ± 2.92 hours and was unusually long compared to term neonates not on ECMO. Since the drug is cleared almost entirely by the kidneys and since several of our patients had elevated serum creatinine concentrations, the increased half-life may have been a function of a reduced glomerular filtration rate in these acutely ill infants. Regardless of the presence of renal injury, however, decreased urine output with resulting oliguria or anuria frequently occurs in neonates on ECMO.

The proposed causes for these changes are many. Dramatic changes in circulating profiles of arachidonic acid metabolites were observed in patients receiving ECMO, together with high plasma renin activity.[15] Elevated blood concentrations of atrial natriuretic factor in these patients also have been reported.[16] These physiologic changes may result in an alteration in total body water and thus a change in gentamicin volume of distribution. There is also a possible

ECMO-related explanation for reduced gentamicin clearance. During V-A bypass, a decrease in pulsatile blood flow to the kidneys may occur. It is possible that the nonpulsatile blood flow could alter renal blood flow patterns and reduce the glomerular filtration rate, and therefore decrease gentamicin clearance. However, the overall effect of this change in flow does not appear to be substantial since (1) the difference in gentamicin half-life between the V-A bypass (10.04 ± 2.45) and V-V bypass (10.75 ± 3.43) infants is not significant, and (2) although urine output and sodium reabsorption decrease with nonpulsatile blood flow, no changes occur in glomerular filtration rate and total renal blood flow.[4] Two other groups also reported prolonged half-life (mean 9.55 and 8.7 hrs, respectively) in infants on ECMO.[12, 13]

Analysis using the two-tailed Student's *t* test indicates that the pharmacokinetics of gentamicin are not significantly different ($p>0.05$) for the two bypass techniques or sizes of oxygenators. It appears that factors other than nonpulsatile blood flow may be responsible for the drug's prolonged half-life. Some possible alternative mechanisms include hypoxic-ischemic injury to the kidneys, shift in intrarenal blood flow, and distribution of gentamicin to compartments other than the central compartment.

Since this was a retrospective study and comparisions were made not with a control group per se, but rather with literature-generated normative values, the potential for a type II error is large; however, calculation of the actual type II error would be inappropriate in a study of this nature. Comparision of gentamicin pharmacokinetics of the ECMO population to a more closely matched group of patients based on severity of illness may demonstrate a less dramatic difference.

Based on the values determined in this study, a recommended initial dosage of gentamicin for neonates receiving ECMO is 2.5 mg/kg every 18 hours. The dosing interval may be more variable and should be determined individually by monitoring serum drug concentrations over time. When ECMO is discontinued, the dosage may require readjustment due to large shifts in body water.

References

1. **Bartlett RH.** Extracorporeal membrane oxygenation in neonates. Hosp Pract 1984;4:139–51.
2. **Extracorporeal Life Support Registry.** Data on file. Ann Arbor: University of Michigan, 1991.
3. **Sisson TRC, Lund CJ, Whalen LE, Telek A.** The blood volume of infants. J Pediatr 1959;55:163–79.
4. **Many M, Soroff HS, Birtwell WC, Wise HM, Deterling RA.** The physiologic role of pulsatile and nonpulsatile blood flow. Arch Surg 1968;97:917–23.
5. **Brans YW, Cornidh JD, Kuehl TJ, Dutton EB, Andrew DS, Menchaca EM.** Effect of extracorporeal membrane oxygenation on body water content and distribution of baboon neonates. Pediatr Res 1986;20:381–4.
6. **Gopler TA.** Continuous arteriovenous hemofiltration in acute renal failure. Am J Kidney Dis 1985;6:373–86.
7. **Thomson AH, Bryson SM, McGovern EM, Kelman AW.** Population pharmacokinetics of gentamicin in neonates. Dev Pharmacol Ther 1988;11:173–9.
8. **Zenk KE, Miwa L, Cohen JL, Waffarn F, Huxtable RF.** Effect of body weight on gentamicin pharmacokinetics in neonates. Clin Pharm 1984;3:170–3.
9. **Szefler SJ, Wynn RJ, Clarke DF, Buckwald S, Shen D, Schentag JJ.** Relationship of gentamicin serum concentrations to gestational age in preterm and term neonates. J Pediatr 1980;97:312–15.
10. **McCraken GH Jr, Jones LG.** Gentamicin in the neonatal period. Am J Dis Child 1970;120:524–33.
11. **Kasik JW, Jenkins S, Leuschen MP, Nelson RM.** Post-conceptional age and gentamicin elimination half-life. J Pediatr 1985;106:502–5.
12. **Southgate WM, DiPiro JT, Robertson AF.** Pharmacokinetics of gentamicin in neonates on extracorporeal membrane oxygenation. Antimicrob Agents Chemother 1989;33:817–19.
13. **Swigart SA, Hoie EB, Willett LD, Nelson RM Jr.** Pharmacokinetics of gentamicin and vancomycin in infants undergoing ECMO. Presented at the 4th annual Children's Hospital National Medical Center ECMO symposium, Snowmass, CO, Feb 21–26, 1988.
14. **Cohen P, Collart L, Prober CG, Fischer AF, Blaschke TF.** Gentamicin pharmacokinetics in neonates undergoing extracorporeal oxygenation. Pediatr Infect Dis J 1990;9:562–6.
15. **Sell LL, Cullen ML, Lerner GR, Whittlesey GC, Shanley CJ, Klein MD.** Hypertension during extracorporeal membrane oxygenation: cause, effect, and management. Surgery 1987; 102:724–30.
16. **Palermo ML, Outwater KM, O'Rourk PP.** Effect of extracorporeal membrane oxygenation on atrial natriuretic factor. Pediatr Res 1989;25:42A.