Evaluation of the Effects of Extracorporeal Membrane Oxygenation on Antiepileptic Drug Serum Concentrations in Pediatric Patients

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OBJECTIVES Patients supported on extracorporeal membrane oxygenation (ECMO) have an increased incidence of seizures. Phenobarbital (PB) and fosphenytoin (fos-PHT) are common antiepileptic drugs (AEDs) used to manage seizures in the pediatric population; however, it is unknown what effect ECMO has on the serum concentrations of AEDs. The purpose of this study is to evaluate the effect of ECMO on AED serum concentrations.

METHODS A retrospective, matched-cohort study was performed in patients younger than 18 years who received ECMO and were treated with intravenous (IV) PB or fos-PHT at Texas Children's Hospital between 2004 and 2014. Patients receiving IV AED therapy and ECMO were matched, based on age, sex, and weight, with patients receiving IV AED therapy without ECMO. The 24-hour cumulative AED dose, serum concentrations, number of doses per serum concentration drawn ratio, volume of distribution, therapeutic serum concentrations, and time to therapeutic serum concentration were compared between both groups. The fos-PHT and PB groups were analyzed in all patients and in neonates only.

RESULTS Fourteen patients met inclusion criteria. The fos-PHT neonatal (20.1 vs 11.3 mg/kg/day, $p = 0.044$), PB composite (33.9 vs 21.6 mg/kg/day, $p = 0.012$), and PB neonatal (40.3 vs 20 mg/kg/day, $p = 0.04$) had larger 24-hour cumulative doses compared with non-ECMO patients. Lower serum concentrations were observed in the PB composite ECMO group (19.1 vs 35.4 mg/L, $p < 0.001$) and the PB neonatal ECMO group (20.5 vs 27.8 mg/L, $p = 0.01$) compared with non-ECMO patients.

CONCLUSION Pediatric patients receiving PB on ECMO and neonatal patients receiving fos-PHT on ECMO required larger doses, and in pediatric patients achieved lower serum concentrations, suggesting the necessity for alternative dosing strategies in these populations.

ABBREVIATIONS AED, antiepileptic drug; ECMO, extracorporeal membrane oxygenation; fos-PHT, fosphenytoin; IV, intravenous; PB, phenobarbital; Vd, volume of distribution

KEYWORDS antiepileptic drugs; extracorporeal membrane oxygenation; fosphenytoin; neonates; pediatrics; phenobarbital

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Introduction

Extracorporeal membrane oxygenation (ECMO), also known as extracorporeal life support, is an invasive cardiopulmonary bypass circuit that is used as temporary support for cardiopulmonary failure. It is used as a bridge to transplantation and for organ recovery for pediatric patients with pulmonary hypertension, sepsis, congenital diaphragmatic hernia, congenital heart disease, cardiac failure, and other less common diagnoses, and it has significantly improved survival rates in pediatric patients.¹

Extracorporeal membrane oxygenation, however, has many risks. Up to 20% of pediatric patients develop a neurologic complication while receiving ECMO, which

significantly increases mortality (62% vs 36%, $p < 0.001$).¹ The incidence of seizures is 9.2% in pediatric patients, and is likely due to complications from anticoagulation, developmental vulnerabilities, and because the primary cannulated vessels are the carotid artery and jugular vein, supplying and draining the cerebral vessels.^{2,3} Treatment of seizures that arise in ECMO patients has traditionally been managed with intravenous (IV) antiepileptic drugs (AEDs), such as phenobarbital (PB) or fosphenytoin (fos-PHT).

Further complicating management in this patient population are the controversial effects of ECMO circuits on the pharmacokinetics of various medications. Extracorporeal membrane oxygenation circuits require

a priming volume between 250 and 400 mL. With total blood volume in pediatric patients ranging between 85 and 105 mL/kg,⁴ the additional volume from the ECMO circuit can greatly affect the volume of distribution (Vd) in patients, even as much as doubling the Vd in smaller patients. Pharmacokinetic studies in pediatric patients have suggested the Vd of PB in pediatric patients not requiring ECMO to be 0.64 to 0.71 L/kg.^{5,6} Two case reports in pediatric patients on ECMO have noted a larger Vd (1.2 L/kg),^{7,8} suggesting a significant alteration to the pharmacokinetic profile of PB in pediatric patients. To date, there have been no studies assessing the Vd of fos-PHT in pediatric patients on ECMO.

Studies in ECMO circuits alone have proposed alterations to pharmacokinetic parameters prior to AEDs reaching the patient. There are conflicting reports regarding drug binding to various ECMO components, such as the large-diameter plastic tubing or the membrane oxygenator. Early studies found up to a 17% reduction in PB concentrations, and up to a 43% reduction in phenytoin concentrations when run through a circuit alone.⁷ Newer data have shown no alteration in PB concentrations and a smaller impact (17.6%–31.4%) on phenytoin concentrations.⁹ The extent to which the drug was lost in these studies was dependent on the duration of circuit use as well as the agent used to prime the circuit.^{7,9} Each study's results vary based on the components used in the ECMO circuit. There is also evolving technology in which different components of the ECMO circuit are being upgraded. This may cause older studies to be less generalizable to pharmacokinetic studies using newer ECMO circuits.

The primary objective of this study was to determine whether ECMO affected AED serum concentrations in pediatric patients. The secondary objective was to describe the current dosing and monitoring trends of AEDs in pediatric patients on ECMO. Additionally, differences between pediatric patients and neonatal patients were explored.

Materials and Methods

Study Design and Population. A retrospective, matched case-cohort study was performed at Texas Children's Hospital, a major pediatric teaching institution in Houston, Texas, between September 1, 2004, and August 31, 2014. Cases were patients younger than 18 years who were initially treated with IV PB or fos-PHT while receiving ECMO. Cases were matched 1:2 based on postmenstrual age at initiation of AED, sex, and weight. Patients who did not have a documented serum PB or phenytoin concentration during ECMO cannulation were excluded. Dose escalation and specific patient target serum concentrations were at the discretion of the medical team. No formal dose escalation strategy was used during the study period. The study was reviewed and approved by Baylor College of Medicine Institutional Review Board.

Data Collection. Electronic medical records were retrospectively reviewed for all patients meeting inclusion criteria. Data extracted from the medical records included: gestational age, postnatal age, weight, sex, ethnicity, primary diagnosis, mode of extracorporeal support, initial AED dosing regimen, maintenance AED dosing regimen, and serum concentrations.

Data and Statistical Analyses. Dosing was characterized as the cumulative dose (mg/kg/day), including maintenance dosing and bolus dosing, within 24 hours of the corresponding serum concentration. Time to serum concentration was characterized as the time from the administration directly before the serum concentration was collected. Subsequent concentrations from the same patient were considered independent occurrences. Therapeutic concentrations for PB and phenytoin are 20 to 40 mg/L and 10 to 20 mg/L, respectively. Time to first therapeutic value was considered the time from the first IV dose to the first serum concentration found to be therapeutic or supratherapeutic for each respective AED. Volume of distribution calculations were performed on patients with at least 2 serum concentrations that were drawn after a single dose.¹⁰ The ECMO circuits were changed during the course of the study; however, specific circuits in use during each case were not available upon review. Neonatal patients were defined as patients less than 44 weeks' postmenstrual age at the initiation of AED. Neonatal patients were analyzed as part of the composite group analysis as well as a separate neonatal group because of an increased expected Vd alteration with the initiation of ECMO compared with older and larger patients. Descriptive statistics were used to characterize the patient population. Differences in patient serum concentrations (mean, SD, median, range) and drug dosing were evaluated between the ECMO and non-ECMO groups using Student *t* test and Fisher exact test. Data analyzed using a Student *t* test were approximately normally distributed. A *p* value of < 0.05 was considered significant.

Results

Demographic and Descriptive Data. A total of 357 patients received ECMO during the study period; 57 patients (16%) received ECMO and AED therapy. A total of 34 patients did not have a documented serum concentration, and 9 received AED doses prior to cannulation on ECMO. A total of 14 of 57 patients (25%) receiving AEDs met inclusion criteria and were included in data analysis. While on ECMO, 3 patients received fos-PHT only, 8 patients received PB only, and 3 patients received both AEDs. There were no significant differences in age (age at AED initiation for composite groups, gestational age, postmenstrual age, or age at AED initiation for neonatal groups), weight, or sex between the ECMO study group and the non-ECMO matched control groups. No patient in the non-ECMO

control group received any type of renal replacement therapy. Demographic and descriptive data of the included samples are given in Table 1.

Diagnoses for the 14 ECMO patients are shown in Table 1. A total of 12 patients (86%) initially received venoarterial ECMO, whereas 2 (14%) received venovenous ECMO. The most common cannulation sites were the common carotid artery (32%) and the internal jugular vein (43%). There were 4 patients (29%) who received continuous renal replacement therapy and 2 patients (14%) who received peritoneal dialysis while on ECMO. Descriptive data for the ECMO group are given in Table 2.

PB Composite Data. The PB composite ECMO group included 11 patients (3 also received fos-PHT). The ECMO and non-ECMO groups had 55 and 54 serum concentrations, respectively. The ECMO group received larger 24-hour cumulative doses (33.9 vs 21.6 mg/kg/day, $p = 0.012$) and had lower serum concentrations (19.1 vs 35.4 mg/L, $p < 0.001$). The ECMO group also had a smaller number of doses per serum concentration drawn ratio (2.2 vs 3.6, $p = 0.048$) compared with the non-ECMO group. There was no difference between time to serum concentration (8.0 vs 7.9 hours, $p = 0.91$) or time to first therapeutic concentration (25.9 vs 23.2 hours, $p = 0.74$). Phenobarbital composite data are summarized in Table 3.

PB Neonatal Data. The PB neonatal (age ≤ 31 days) ECMO group included 5 patients. The ECMO group and non-ECMO group had 31 and 19 serum concentrations, respectively. The ECMO group received larger 24-hour cumulative doses (40.3 vs 20 mg/kg/day, $p = 0.04$) and had lower serum concentrations (20.5 vs 27.8 mg/L, $p = 0.01$). There were no differences in number of doses per serum concentration drawn ratio in the ECMO group (2.2 vs 4.2, $p = 0.09$) or time to serum concentration (7.9 vs 8.2 hours, $p = 0.89$). The PB neonatal pharmacokinetic data are summarized in Table 3.

Fos-PHT Composite Data. The fos-PHT composite ECMO group contained 6 patients (3 also received PB). Each group had 23 serum phenytoin concentrations. There were no significant differences between the ECMO and non-ECMO groups. The fos-PHT composite pharmacokinetic data are summarized in Table 3.

Fos-PHT Neonatal Data. The fos-PHT neonatal ECMO group included 3 patients. There were 17 serum phenytoin concentrations for the ECMO group and 11 serum concentrations for the non-ECMO group. The ECMO group received a larger 24-hour cumulative dose (20.1 vs 11.3 mg/kg/day, $p = 0.044$). There were no differences between serum concentrations (8.4 vs 7.3 mg/L, $p = 0.55$) or time to serum concentration (9.8 vs 7.1 hours, $p = 0.23$) between the groups. Fos-PHT neonatal pharmacokinetic data are summarized in Table 3.

Discussion

Even though we evaluated only 14 patients, to our

Table 1. Demographic Data in Patients on Extracorporeal Membrane Oxygenation (ECMO)

Parameter	n (%)
Diagnosis	
Congenital diaphragmatic hernia	3 (21)
Pulmonary hypertension	2 (14)
Respiratory failure	3 (21)
Pulmonary atresia	3 (21)
Septic shock	1 (7)
Hypoplastic left heart	1 (7)
Hypoxic ischemic encephalopathy	1 (7)
Mode of ECMO	
Venoarterial	9 (64)
Venovenous	2 (14)
Emergent	3 (21)
ECMO cannulation site	
Carotid	9 (32.1)
Jugular	12 (42.9)
Atria	3 (10.7)
Aorta	3 (10.7)
Femoral	1 (3.6)
Renal replacement	
Peritoneal dialysis	2 (14.3)
Continuous renal replacement	4 (28.6)
None documented	8 (57.1)
Ethnicity	
Hispanic, white	7 (50)
Non-Hispanic, black	1 (7)
Non-Hispanic, white	4 (29)
Unknown	2 (14)
Year of treatment	
2007	5 (35.7)
2008	2 (14.3)
2009	2 (14.3)
2012	5 (35.7)

knowledge this is the largest study evaluating the effects of ECMO on AED serum concentrations in pediatric patients. Limited case reports have described drug disposition in ECMO patients receiving PB.^{8,11} Each case report had different dosing strategies, used different ECMO circuits, and achieved different results.

The ECMO group patients received significantly larger doses of PB and obtained significantly lower serum concentrations than their non-ECMO counterparts. This difference was seen in composite patients and in the neonatal group. Although there was not an

Table 2. Descriptive Data of Patients Receiving Fosphenytoin or Phenobarbital With or Without Extracorporeal Membrane Oxygenation (ECMO)

Demographics	ECMO	Non-ECMO	p value
Fosphenytoin composite group			
No. of patients	6	12	
Age at initiation, days*	205.9	221.0	0.93
Weight, kg*	6.1	6.2	0.98
Male sex, n (%)	4 (67)	8 (67)	1
Phenobarbital composite group			
No. of patients	11	22	
Age at initiation, days*	151.5	156.6	0.96
Weight, kg*	151.5	156.6	0.96
Male sex, n (%)	7 (64)	14 (64)	1
Fosphenytoin: neonates			
No. of patients	3	6	
GA, wk*	38.0	39.4	0.09
PMA, wks*	39.9	41.4	0.46
Age at initiation, days*	13.3	13.7	0.97
Weight, kg*	4.0	4.3	0.50
Male sex, n (%)	2 (67)	4 (67)	1
Phenobarbital: neonates			
No. of patients	5	10	
GA, wk*	39.1	38.9	0.78
PMA, wk*	40.4	40.1	0.76
Age at initiation, days*	9.0	7.7	0.69
Weight, kg*	3.0	3.3	0.35
Male sex, n (%)	3 (60)	6 (60)	1

GA, gestational age; PMA, postmenstrual age

* Mean.

association with delayed time to therapeutic serum concentration associated with these differences, there was a significant decrease in the number of doses per serum concentration drawn. This suggests that these patients may have received more frequent one-time doses, more frequent dose adjustments, and were more challenging to manage.

There were no differences in serum phenytoin concentrations or doses between the 2 fos-PHT composite groups. However, there was a significant increase in the required dose for neonatal ECMO patients to achieve serum phenytoin concentrations similar to those of their non-ECMO counterparts, but the number of patients was small. Perhaps neonates may be more influenced by the alterations in pharmacokinetics seen with ECMO initiation and may require larger expected doses to achieve serum concentrations similar to those of their non-ECMO counterparts.

Although seizure control is the primary focus of AED

therapy in patients who have seizures, this study did not assess seizure frequency or control. Because the ECMO study group was heavily sedated and, in some instances, also receiving neuromuscular blockade, seizure frequency could only reliably be assessed with continuous electroencephalogram, which was not always performed.

The ECMO group was more likely to receive one-time unscheduled doses than the non-ECMO group. This could potentially be due to concern for hemodynamic instability in these critically ill patients who receive larger doses of AEDs. Although titrating AEDs until seizures are controlled is common practice, expecting ECMO patients to require larger doses, as we observed, may allow clinicians to be more aggressive in adjusting doses. This may require weighing the risks and benefits of escalating doses more quickly on a case-by-case basis, even in those patients with hemodynamic instability.

In composite groups, there were inconsistencies

Table 3. Extracorporeal Membrane Oxygenation (ECMO) Outcomes

ECMO Outcomes	ECMO	Non-ECMO	p value
Fosphenytoin composite group			
No. of patients	6	12	
Dose, mg/kg/day*	20.5	20.8	0.93
Serum concentration, mg/L*	10.5	12.0	0.45
Time to serum concentration, hr*	8.0	6.4	0.32
Volume of distribution, L*	6.4	6.9	0.88
No. of doses per serum concentration drawn*	2.7	5.8	0.23
Time to first therapeutic serum concentration, hr*	14.9	14.1	0.93
Subtherapeutic, n (%)	12/23 (52)	10/25 (40)	0.56
Fosphenytoin neonatal group			
No. of patients	3	6	
Dose, mg/kg/day*	20.1	11.3	0.04
Serum concentration, mg/L*	8.4	7.4	0.56
Time to serum concentration, hr*	9.8	7.1	0.23
Volume of distribution, L*	7.2	4.9	0.68
No. of doses per serum concentration drawn*	3.8	9.5	0.20
Time to first therapeutic serum concentration, hr*	29.9	22.0	0.78
Subtherapeutic, n (%)	12/17 (71)	8/11 (73)	1
Phenobarbital composite group			
No. of patients	11	22	
Dose, mg/kg/day*	33.9	21.6	0.01
Serum concentration, mg/L*	19.1	35.4	<0.001
Time to serum concentration, hr*	8.0	7.9	0.91
Volume of distribution, L*	2.2	1.6	0.10
No. of doses per serum concentration drawn*	2.2	3.6	0.05
Time to first therapeutic serum concentration, hr*	25.9	23.2	0.74
Subtherapeutic, n (%)	30/55 (55)	4/54 (7)	<0.001
Phenobarbital neonatal group			
No. of patients	5	10	
Dose, mg/kg/day*	40.3	20.0	0.04
Serum concentration, mg/L*	20.5	27.8	0.01
Time to serum concentration, hr*	7.9	8.2	0.89
Volume of distribution, L*	1.7	1.0	0.41
No. of doses per serum concentration drawn*	2.2	4.2	0.09
Time to first therapeutic serum concentration, hr*	25.6	22.7	0.81
Subtherapeutic, n (%)	14/31 (45)	4/19 (21)	0.13

* Mean

regarding the timing of when serum concentrations were obtained, because this study was a retrospective and timing of serum concentrations was clinically determined. Because the study population included patients from the pediatric intensive care unit, cardiovascular

intensive care unit, and neonatal intensive care unit, there was service variability in dosing strategies' timing of AED levels. It may still be necessary to ensure that the medical teams, regardless of the service, obtain serum concentrations at consistent times in the future.

There were some limitations to this study. First, the sample size was small; however, this is the largest study to date evaluating the effect of ECMO on AEDs in pediatric patients. Second, variations in timing of serum concentrations make it difficult to draw definitive conclusions about dosing strategies and serum concentrations between groups. Although there were clear differences seen between the groups, the impact of variable serum concentration timing is unknown. Third, this was a retrospective study, and data collection was dependent on the accuracy of information provided in the electronic medical record. The study was carried out during the course of 10 years, and during that time there were changes in the ECMO guidelines and clinical practices, as well as changes in the ECMO circuits used. Patients were also not matched on diagnoses, providing a potential confounder in baseline differences between the ECMO and non-ECMO study groups. Additionally, 43% of cases received renal therapies in addition to ECMO (therapies that could remove drug), compared with none of the non-ECMO patients.

Future directions include the development of alternative dosing strategies to ensure timely administration, and knowledge that larger cumulative doses are required to obtain proper serum concentrations. There also is the opportunity for improvement to educate clinicians regarding the importance of obtaining serum AED concentrations. Because levetiracetam is being used more commonly as first-line therapy for seizures, it will be important to assess the effects of ECMO on levetiracetam pharmacokinetics, in addition to other medications used in ECMO patients.

Conclusion

Pediatric patients experience alterations to their pharmacokinetics of PB and fos-PHT while receiving ECMO, which may necessitate alternative dosing strategies in order to achieve adequate serum concentrations. This study showed pediatric ECMO patients who received PB required larger doses that resulted in decreased serum concentrations. Development of alternative dosing strategies for AEDs in pediatric patients on ECMO may allow health care practitioners to achieve adequate serum concentrations with less frequent dose adjustments and one-time bolus administrations.

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