

# Phenobarbital use in an infant requiring extracorporeal membrane life support

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## Abstract

Over the past two decades, there has been an increased use of extracorporeal membrane life support (ECLS) for critically ill neonates and infants. Approximately 20% of these children will experience seizures as a complication of ECLS or the comorbid condition which necessitated extracorporeal support. While phenobarbital is one of the most common drugs used to treat seizures in children, little is known about its dosing while on ECLS. We present a 3-month-old girl who required ECLS after cardiac arrest in the postoperative period following surgery for complex congenital heart disease. The patient subsequently developed seizure activity, which was treated with phenobarbital. Following an initial loading dose of 30 mg/kg, the serum concentration was 47.9 mcg/ml. A supplementary loading dose of 10 mg/kg was administered 8 h later with an increase of the maintenance dose to 8 mg/kg/day. The phenobarbital serum concentrations were 65.9 and 72.8 mcg/ml on the subsequent days. Despite therapeutic levels of phenobarbital, the patient continued to exhibit clinical and electroencephalographic evidence of seizure activity and a midazolam infusion was started at 0.3 mg/kg/h. Because of continued seizure activity, the patient ultimately required titration of midazolam to 1.2 mg/kg/h by day 7 of ECLS to control seizure activity. Due to severe intracerebral bleeding on day 9, ECLS was withdrawn and the patient expired. Our experience demonstrates some of the challenges of medication titration during ECLS. Previous reports of phenobarbital dosing during ECLS are reviewed and considerations for the dosing of anticonvulsant medications during extracorporeal support are discussed.

**Key words:** Extracorporeal membrane life support, pediatric anesthesia, phenobarbital

## Introduction

Over the past two decades, there has been an increased use of extracorporeal membrane life support (ECLS) for critically ill neonates and infants.<sup>[1,2]</sup> While receiving ECLS, critically ill patients may require the administration of several medications to treat comorbid conditions, including seizures.<sup>[3]</sup> In current practice, phenobarbital is frequently chosen as an anticonvulsant in neonates and young infants.<sup>[4-6]</sup> Although dosing regimens have been well established in this population, there are limited data regarding changes in dosing imposed

by the use of ECLS devices. We present a 3-month-old, 4.11 kg infant who had a cardiac arrest following surgery for complex congenital heart disease (CHD) requiring the institution of ECLS and the administration of phenobarbital to control seizure activity. Previous reports of phenobarbital dosing during ECLS are reviewed and considerations for the dosing of anticonvulsant medications during extracorporeal support are discussed.

## Case Report

Institutional Review Board approval is not required at Nationwide Children's Hospital for the presentation of single case reports. A 3-month-old, 4.11 kg infant was admitted to the cardiothoracic intensive care unit following atrial septectomy and pulmonary artery banding for complex CHD. On the evening following surgery, the patient experienced a sudden cardiopulmonary arrest which was unresponsive to conventional resuscitation efforts and was placed on ECLS (prime volume = 417 ml). On day 2 of ECLS, the patient developed twitching of her left upper extremity with electroencephalographic (EEG) features consistent with seizure activity. At that time, computed

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tomography (CT) scan of the head was normal. Given the absence of structural abnormality on CT and the lack of metabolic abnormalities, the cause of seizure was attributed to hypoxic brain injury. Following an initial phenobarbital loading dose of 30 mg/kg, the serum concentration was 47.9 mcg/ml. At the time an albumin level was shown to be 3.2 g/dl. As the goal per the recommendations of pediatric neurology was to achieve a serum concentration of 60 mcg/ml, a supplementary loading dose of 10 mg/kg was administered 8 h later with an increase of the maintenance dose to 8 mg/kg/day. The phenobarbital serum concentrations were 65.9 and 72.8 mcg/ml on the subsequent days. Despite therapeutic levels of phenobarbital, the patient continued to exhibit clinical and EEG evidence of seizure activity. A midazolam infusion was started at 0.3 mg/kg/h. Because of continued seizure activity, the midazolam infusion was increased to 1.2 mg/kg/h by ECLS day 7. On the morning of ECLS day 9, the patient was noted to have an enlarged right pupil. Given the acute change in neurologic exam, a second CT scan of the head was done, which showed bilateral subdural hematomas with hypoxic encephalopathy. Given the complexity of transporting a patient on ECLS and the unchanged neurologic exam, no interval CT scans had been done between days 2 and 9. The family was consulted regarding the patient's poor prognosis and comfort care was initiated. Hemodynamic and respiratory support was removed and the patient expired with the family at the bedside.

## Discussion

Approximately 20% of infants receiving ECLS develop seizures.<sup>[3]</sup> While the etiology of this complication is often multifactorial, phenobarbital has traditionally been used given its established history of efficacy.<sup>[4-6]</sup> Despite its frequent and increasing use in critically ill patients, there are limited data regarding dosing alterations that are required in patients undergoing ECLS.<sup>[7]</sup> When considering such patients, both technology (ECLS) and patient related factors must be considered. Major considerations include prime volume, serum protein dilution, circuit absorption, and elimination altering organ dysfunction. Regardless of the medication used, significant alterations in the plasma concentration and hence the clinical effect can be induced by the institution of ECLS techniques. While few trials exist which help to guide drug dosing on ECLS, a trend has emerged demonstrating a larger volume of distribution and extended elimination time while on ECLS.<sup>[8-12]</sup>

Following cannulation and the institution of ECLS, an increased volume of distribution can be expected related to the large priming volume of the circuit. Even with improvements

in the technology with smaller prime volumes, a doubling of the effective circulating blood volume will occur. In our patient with a body weight of 4.11 kg, the effective blood volume was doubled with the circuit volume of 417 ml. The larger volume of distribution was demonstrated by the larger loading dose. The initial dose of 30 mg/kg in a serum concentration of 47.9 mcg/ml with an additional dose of 10 mg/kg (total dose of 40 mg/kg) required to achieve a concentration of 65.9 mcg/ml.

Similarly, Elliot and Buck reported their experience with phenobarbital dosing in a newborn with a congenital diaphragmatic hernia before, during and after ECLS.<sup>[13]</sup> Although seizure activity was controlled by a standard loading dose of 20 mg/kg, the serum concentration was below the desired concentration (16.4 mcg/ml at 3 h and 12.9 mcg/ml at 24 h). A standard maintenance dose of 5 mg/kg/day maintained these concentrations. The volume of distribution was estimated at 1.2 l/kg while the elimination was 77.1 h. The authors concluded that the volume of distribution was larger than published parameters in neonates while the elimination half-life was similar.

Although the primary cause of the larger volume of distribution has been attributed to the increased volume related to the circuit, other factors may play a role including fluid disturbances related to the underlying pathology, altered protein binding, and loss of drug in the ECLS circuit itself via sequestration or absorption. Loss of drug in the ECLS circuit has been previously described although its mechanisms remain poorly understood.

With respect to absorption, Dagan *et al.* studied several medications in an *in vitro* ECLS model.<sup>[14]</sup> The authors noted significant reductions in phenobarbital, gentamicin, morphine, and vancomycin concentrations after flow through the oxygenator component of the circuit. Drug loss was minimal through a circuit that had been used for 5 days in a patient. The authors concluded there is an eventual saturation of binding sites on the circuit (membrane oxygenation) after continued use.

More recent work has demonstrated that the absorbance of the drug correlates directly with its lipophilicity.<sup>[15]</sup> When considering other medications that may be used as anticonvulsants in the critically ill child, midazolam also shows significant binding to the oxygenator with differences noted related to the type of pump and the type of oxygenator.<sup>[15]</sup> The recovery of midazolam in centrifugal pump circuits with hollow-fiber membrane oxygenator was significantly higher compared to neonatal roller pump circuits with silicone membranes. The significant increase in midazolam infusions that may occur is clearly demonstrated in our patient with dose requirements starting at 0.3 mg/kg/h

and increasing up to 1.2 mg/kg/h to achieve the desired therapeutic effect.

Although used less frequently than phenobarbital, phenytoin and fos-phenytoin may be used in the treatment of seizures in neonates and infants. As with other medications, a significant decline (43%) in phenytoin plasma concentrations was noted due to absorbance to the oxygenator. Additionally, as with other medications, an increase in the volume of distribution should be expected, thereby mandating use of a larger loading dose.<sup>[14]</sup> Other investigators have demonstrated a 15.6% decrease in the fos-phenytoin concentration in a crystalloid-primed circuit and a 33.7% decrease in a blood-primed circuit.<sup>[16]</sup>

The mechanisms accounting for decreased drug elimination during ECLS are slightly less clear. Deranged renal function seems to be a reasonable explanation as renal blood flow, glomerular filtration, and urine output are frequently decreased while on ECLS.<sup>[17]</sup> The lack of pulsatile flow is a frequently cited mechanism although patients receiving veno-venous ECLS with preserved pulsatile flow have similar degrees of renal dysfunction.<sup>[18]</sup> Others postulated mechanisms include the release of vasoactive substances such as arachidonic acid and renin. Furthermore, tissue hypoxia prior to the institution of ECLS related to hypoxemia or decreased perfusion likely contributed not only to renal dysfunction, but also hepatic dysfunction which may further alter drug elimination.

In summary, various factors can significantly alter the pharmacokinetic of commonly used anticonvulsant medications during ECLS. These may include both patient-related and circuit-specific issues. In general, a significant increase in the volume of distribution is noted necessitating the use of a larger loading dose. In most instances, decreased elimination has been reported. The increased volume of distribution is clearly related to the priming volume of the circuit and medication binding to the oxygenator. Differences in the magnitude of the effect have been shown to correlate with the lipophilicity of the drug, type of pump, type of oxygenator, and site of injection of the medication. Most importantly, significant and abrupt decreases in the serum concentration may occur should it be necessary to switch the circuit or change out the oxygenator. Given the interplay and variability of these factors combined with patient related issues of end-organ dysfunction which further impact drug elimination, our recommendation would be to use medications that allow for plasma concentration monitoring. Alternatively as was done in our case, we chose to use a midazolam infusion with titration against a clinical monitor (continuous EEG monitor).

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