Levetiracetam use during extracorporeal membrane oxygenation in an adolescent patient

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Abstract
Extracorporeal membrane oxygenation (ECMO) is a form of advanced life support which is reserved for respiratory or cardiac failure. Drug properties are affected and there are limited studies of medication use in this form of life support. We describe the case of a 16-year-old male deployed on ECMO for refractory respiratory failure who was receiving levetiracetam for seizures. A pharmacokinetic study was performed to determine drug levels through different points in the ECMO circuit and in the patient. Pharmacokinetic parameters were similar in healthy pediatric patients suggesting that ECMO does not affect the pharmacokinetic parameters of levetiracetam. To the authors’ knowledge, this is the first report of levetiracetam use during ECMO in a pediatric patient.

Key words: Extracorporeal membrane oxygenation, levetiracetam, seizure, respiratory failure.

Introduction
Extracorporeal membrane oxygenation (ECMO) is a form of pulmonary and cardiac life support reserved for refractory critical illness. (1) Essentially a bypass mechanism, it consists of extensive tubing, a centrifugal pump, a membrane oxygenator, plus or minus a dialysis filter. (2,3) Each of these components can affect drug pharmacokinetics as they can act as drug reservoirs. (1) Levetiracetam is an antiepileptic medication with a poorly understood mechanism of action. It interacts with synaptic vesicle protein 2A, inhibits voltage dependent calcium channels, among various other proposed actions. (4,5) It has excellent absorption, a quick onset of action, and low drug interactions. (6) It is excreted mainly unchanged in the urine. (6) From pediatric studies dosing of 20-60 mg/kg/day produce approximate adult pharmacokinetic values such as a clearance of 1-1.5 ml/min/kg and half-life of 4-6 hours. (6,7)

Patient case
We report a 16-year-old, 65 kg male with no significant past medical history transferred after two weeks of critical illness to our level one medical-surgical Pediatric Intensive Care Unit (PICU) for continued management of refractory hypoxic respiratory failure and potential ECMO support. His illness began with attempted intoxication by ingestion of a combination of baclofen, promethazine, alcohol, and marijuana. During his two week course at the referring facility he required ventilation with an oscillator and nitric oxide with subsequent weaning to a conventional ventilator prior to transport to our facility. On the day of admission to the outside hospital he experienced a generalized tonic clonic seizure for which he received lorazepam, levetiracetam, and fosphenytoin. The fosphenytoin was discontinued before transfer to our ICU. On day 13 of his stay at our hospital, day 31 post ingestion, worsening hypoxia and air leak syndrome led to elective placement of the patient on venovenous (VV) ECMO.
via right internal jugular vein. A Sorin CP5® (revolution cone) with a Maquet Quadrox® oxygenator and Sorin® tubing was used for ECMO. The flow was set at 2235 revolutions per minute with an average blood flow of 4 L/min. A dialysis filter was not attached to the circuit as the patient had a serum creatinine of 0.4 mg/dL and a urine output of >1 ml/kg/hr.

The patient was continued on levetiracetam 500 mg intravenous every 12 hours while on ECMO with no clinical seizure activity. On day 13 of ECMO, an EEG was performed and showed no signs of seizure activity. The agent, levetiracetam, was delivered over 15 minutes at a concentration of 15 mg/ml through a triple lumen femoral central venous catheter. Since the patient had been on levetiracetam since admission, steady state drug concentration was achieved. Levetiracetam trough levels were drawn 12 hours after the start of the infusion and peak levels obtained one hour after the start of infusion. The two ports on the ECMO circuit were accessed immediately prior to and post oxygenator. Peak levels were drawn 30 minutes after the end of the levetiracetam infusion from the same three sites. Blood samples were sent to a reference laboratory where quantitative enzyme immunoassay was performed. (8) Patient trough level was 27 micrograms/ml and peak level of 44 micrograms/ml with similar values at the two ECMO sites (Table 1). The elimination rate constant (k_e) was 0.044 h⁻¹; elimination half life (T₁/₂) was 15.6 hrs; volume of distribution (V_d) was 0.45 L/kg; and clearance was 1.39 L/hr (0.33 ml/kg/min).

**Discussion**

To our knowledge this is the first documented case report of levetiracetam use during ECMO in a pediatric patient. In a recent case, a 67-year-old man was placed on continuous renal replacement therapy (CRT) and ECMO secondary to a large right coronary artery infarct. Levetiracetam was given and multiple drug levels obtained. The authors reported a V_d of 0.65 L/kg and a T₁/₂ of 8.7-10.1 hours and concluded that pharmacokinetics on ECMO and CRT are similar in healthy adult patients. (9)

In our case we sought to quantify the ability of ECMO to remove drug from the blood. By obtaining levels from the patient and from two points on the circuit we were able to determine that no drug was removed due to the membrane oxygenator or from the complete ECMO circuit. The slight differences (less than 10%) in our laboratory values can be attributed to variability in blood sampling and laboratory evaluation. Through laboratory information and email communication with J. Mohlman, MD, MPH (Jeffrey.mohlman@arulab.com, ARUP Laboratories) (September 2015), specific laboratory variability can range from 6-10% for this specific test. (8) The pharmacokinetic parameters determined from the levels obtained correlate with the typical parameters of healthy pediatric patients and adult critical care patients. (6,7,10) The elimination T₁/₂ and clearance in our case was slightly higher than healthy pediatric patients most likely due to decreased glomerular filtration that can occur as a result of ECMO deployment. (1) The levels obtained in our patient are within the reported range of 12-46 micrograms/ml suggesting that standard dosing should be applied for patients undergoing ECMO. (11)

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<tr>
<th>Table 1. Six levetiracetam levels in micrograms per ml</th>
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<tr>
<td>Trough</td>
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<td>Patient femoral line</td>
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Legend: Trough levels were obtained 12 hours after start of the prior infusion and peak levels obtained one hour after the start of infusion. The two ports on the ECMO circuit were accessed immediately prior to and after the oxygenator.
References