

The Impact of Extracorporeal Life Support and Hypothermia on Drug Disposition in Critically Ill Infants and Children

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KEYWORDS

- Infant • Extracorporeal membrane oxygenation • Sedation • Analgesia
- Pharmacology • Pharmacokinetics • Pharmacodynamics • Hypothermia

KEY POINTS

- Extracorporeal membrane oxygenation (ECMO) increases volume of distribution and reduces clearance of most drugs.
- Lipophilic drugs in particular are sequestered by the ECMO circuits.
- Sequestration of drugs is to a large extent circuit dependent.
- Hypothermia influences volume of distribution and decreases clearance.
- Hypothermia superimposed on ECMO most likely decreases clearance further, especially for drugs with a high hepatic clearance.
- Therapeutic drug monitoring is recommended for drugs with a small therapeutic window.

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INTRODUCTION

Extracorporeal life support (ECLS) or extracorporeal membrane oxygenation (ECMO) is a technique providing life support in severe but potentially reversible cardiorespiratory failure in patients with an expected mortality greater than 80%.¹ ECLS has been used as prolonged cardiopulmonary support in neonates since 1976² with a proven survival benefit in neonates and adults.^{3,4}

ECMO provides extracorporeal gas exchange and circulatory support by pumping blood from the patient through an artificial circuit comprising tubing, a pump, an oxygenator, and a heater. The oxygenator is used to oxygenate the blood and extract carbon dioxide. Blood is drawn from a venous access site, preferably a central catheter positioned in the right atrium, and returned either into the right atrium via a double-lumen catheter (venovenous ECMO) for respiratory support or via the carotid artery (venoarterial ECMO) for cardiopulmonary support.

Up to July, 2011, 46,509 patients worldwide have received ECMO support, including 29,839 neonates, 11,779 pediatric patients, and 4891 adult patients (Extracorporeal Life Support Organization registry report, July, 2011). ECMO support is used in a variety of diagnoses in the pediatric population. Cardiac failure is the primary reason for ECMO in 45% of all cases. Diagnoses include cardiopulmonary resuscitation (CPR), cardiomyopathy, cardiomyositis, postcardiothoracic surgery, and sepsis. Pulmonary failure caused by viral or bacterial pneumonia and acute respiratory distress syndrome constitutes the major cause for pulmonary ECMO support. In 10% of all cases, ECMO was initiated during the course of CPR. There are increasing reports of ECMO in severe accidental hypothermia and prolonged refractory CPR.^{5–10}

Although it may be lifesaving in critically ill patients, ECMO treatment is associated with several complications and mortality. Overall survival after ECMO support is 62%, and mortality is primarily associated with the underlying disease and complications of/during ECMO such as bleeding, renal failure, and infections.^{11–15} Prolonged ECMO support (>10 days) is associated with increased complications (such as nosocomial infections^{16–25}) and poor outcome.^{15,26}

Neurologic complications are frequent in ECMO patients, with intracranial hemorrhage, infarction, or seizures occurring in 7.4%, 5.7%, and 8.4% of all ECMO patients.²⁷

Therapeutic hypothermia is an established therapy to prevent secondary neurologic damage in adults after cardiac arrest as well as in neonates after severe asphyxia.^{28–34} The use of therapeutic hypothermia in the pediatric setting remains controversial.^{35–37} However, several small studies have explored feasibility and safety of therapeutic hypothermia in the pediatric population.^{38–40} At least 1 study included ECMO patients.³⁸ There are several publications of sustained therapeutic hypothermia in both neonates and infants during ECMO, showing that it is at least feasible.^{38,41–44} Although randomized controlled trials (RCTs) in the pediatric setting are lacking, the resuscitation guidelines of the American Heart Association state that mild hypothermia may be considered in children who remain comatose after resuscitation.⁴⁵ An RCT evaluating standard hypothermia in neonates on ECMO is being conducted in the United Kingdom to evaluate the effect of hypothermia on neurologic outcome.⁴¹ Hypothermia is used in pediatric postresuscitation patients awaiting RCTs, including ECMO patients.

Pharmacokinetic Changes in ECMO

The use of ECMO is associated with major pharmacokinetic (PK) and pharmacodynamic (PD) changes.^{46–49} Patients on ECMO generally receive more than 10 different

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