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

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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 doublelumen catheter (venovenous ECMO) for

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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 (Extra-corporeal 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 drugs per day.⁵⁰ These patients are heparinized to prevent clotting of the ECMO circuit, receive sedatives and analgesics to alleviate pain and discomfort, diuretics to manage fluid overload, and antibiotics or antiviral medication to treat infections.⁵⁰

ECMO increases the circulating volume of the patient because of the added blood volume necessary to fill the circuit. Total circulating volume may be increased by 5% to more than 100% depending on patient and circuit size. The added volume influences blood composition, coagulation, circulation, and PK. Decreased protein levels, especially albumin, increase the unbound fraction of protein-bound drugs, thereby influencing volume of distribution (Vd) and total body clearance (Cl). Depending on the ECMO mode, organ perfusion and organ function are altered, which alters drug absorption, distribution, metabolism, and elimination.⁴⁶

Profound changes in amount and composition of drug-metabolizing enzymes, organ function, and body composition take place in early infancy. Both total body water and extracellular water content change rapidly within the first months of life. Changes in body water and body fat are most dramatic in the first year of life but continue up to puberty. This situation results in age-specific and drug-specific PK changes.^{51,52} Both hepatic and renal Cl are subject to changes in the first month of life. Hepatic metabolism via cytochrome P450 (CYP) and uridine diphosphate glucuronosyltransferase (UGT) are markedly different in the newborn period compared with the pediatric and adult population. Most CYP enzymes reach mature levels at 1 year of age, with higher than adult levels in children younger than 10 years. Renal Cl increases from the newborn period to mature values in the first year of life.⁵²

Patients on ECMO are critically ill, which in itself changes PK and PD.^{53–55} CYP enzymes are downregulated during inflammation, resulting in reduced Cl of drugs cleared by the liver.^{56–58} ECMO increases the inflammatory response by activating inflammatory cytokines, which could further decrease CYP metabolism.⁵⁹ Whether ECMO patients differ in this regard compared with patients who are critically ill but not on ECMO remains to be determined.

These changes should be taken into account when evaluating PK changes during ECMO treatment in the pediatric population.

A recent review⁴⁶ has evaluated the changes in PK and PD during ECMO. With the use of nonlinear mixed modeling (NONMEM) and liquid chromatography mass spectrometry (LC-MS), sparse sampling strategies are used to assess PK in infants on ECMO. Most available studies show altered PK with changes in Vd as well as Cl.^{60–74} Typically, Vd is increased between 5% and 400% for most drugs, whereas Cl is decreased between 0% and 50% compared with patients who are not on ECMO, resulting in prolonged elimination half-life.⁴⁶

A major factor in the changed Vd is adsorption of drugs within the ECMO system components. Several studies have reported drug loss up to 99% for some drugs in in vitro setups. Lipophilic drugs in particular are sequestered to a high degree by the ECMO circuit,^{75–83} with a strong correlation between lipophilicity expressed as logP and adsorption rates.⁷⁷ There is a large difference in adsorption rates between silicone-based membranes and microporous membranes.^{77,83} The use of newer circuits with microporous membranes may result in markedly different PK profiles in patients. New systems such as the iLA Active ECMO circuit (Novalung, Hechingen, Germany) are being used in the pediatric

population (Wildschut, personal communication, 2012). It is unclear how these newer systems and oxygenators affect drug disposition.

Incorporating continuous renal replacement therapy into the ECMO circuits influences drug disposition by increasing hemodilution and drug sequestration. Depending on water solubility, molecule size and protein-binding drugs can be cleared via hemofiltration or dialysis.⁸⁴ The unbound fraction can be used as a crude estimation for the sieving coefficient and the subsequent expected effect of hemofiltration.⁸⁴ Therefore, CI may be increased for these drugs during dialysis, whereas for other drugs it may be decreased.

Although there are increasing data on PK changes, we are still limited by sparse data and small data sets, which make it difficult to effectively predict PK for our patients. Most PK data are from neonatal studies with large ECMO circuits consisting of PVC tubing and silicone-based membranes.

PK Changes in Hypothermia

Hypothermia is associated with significant changes in physiology as well as absorption, distribution, and elimination of drugs. As a consequence, changes in PK and PD may occur.^{47–49} A recent review by van den Broek and colleagues⁴⁷ summarized the studies on changes in PK and PD during hypothermia in animals, adults, and children.

Hypothermia decreases cardiac output⁸⁵ and changes organ perfusion by redistribution of blood flow from the extremities, kidneys, and liver to the brain and heart. Furthermore, intravascular volume is decreased by hemoconcentration, thereby influencing PK.^{86–88} Renal blood flow is also decreased during hypothermia in animal studies. Elimination of drugs by glomerular filtration subsequently decreases. It is unclear if tubular excretion and reabsorption are affected as well.⁴⁷

Hypothermia changes the solubility of carbon dioxide in blood. When blood samples are not corrected for patient temperature (alpha-stat method) the patient P_{CO_2} (partial pressure of carbon dioxide) is lower by 0.82% compared with the measured value, with a subsequent higher pH than the obtained value. Potentially, there is a risk of higher pH values during hypothermia if clinicians use normal P_{CO_2} and pH targets and blood gas analysis without temperature correction (pH-stat method).⁸⁹ Ionization of drugs may be altered by changes in pH. The Vd of drugs with pK_a between 7 and 8 may be altered. Weak bases show an increased Vd and weak acids show decreased Vd when pH is not corrected. Lipid solubility is affected by temperature as well. Lower temperature decreases lipid solubility, thereby influencing Vd for lipophilic drugs. The effects on overall PK is probably small in mild hypothermia (32–34°C).⁴⁷

Overall, ECMO seems to increase Vd, whereas the effects of hypothermia result in decreased Vd for most drugs.

Both ECMO and hypothermia seem to decrease renal and hepatic drug CI. Combining ECMO and hypothermia may result in increased plasma levels and subsequent adverse effects. During rewarming, changes may reverse and may be even more profound in the ECMO population compared with the non-ECMO population.

PK Changes in Cardiopulmonary Bypass

There are no PK or PD data in ECMO patients during hypothermia, in the adult, pediatric, or neonatal population. However, by combining the available data, including PK data, during hypothermic cardiopulmonary bypass (CPB), we have tried to predict the possible effects on the PK of several drugs in the pediatric ECMO population. A recent review summarized the available PK data in pediatric and adult patients during CPB. (van Saet, 2012, submitted for publication).

CPB is significantly different from ECMO not only in duration (hours vs days) and system size but also in the use of mild to deep hypothermia (normally 34°C down to 18°C) and circulatory arrest or selective brain perfusion. Cardiac output or flow rates during ECMO may be significantly different from those targeted during hypothermic CPB, thus changing organ perfusion and subsequent organ function. PK in CPB may therefore be markedly different compared with PK during ECMO and should be translated to the ECMO population with caution.

However, the comparison of PK between normothermic and hypothermic CPB may give vital clues in PK changes caused by hypothermia during ECMO. Table 1 gives an overview of the general effects of ECMO, CPB, and hypothermia on PK parameters. The next section discusses possible changes in PK or PD of different drugs in infants on ECMO. The changes for individual drugs are summarized in Table 2.

Sedative and Analgesic Drugs

Data on sedation and analgesia in ECMO patients are available only from newborn studies. Higher needs of sedative drugs have been reported for these patients.^{110,112,127,145} Midazolam, fentanyl, and morphine are the drugs most commonly used and studied in the ECMO population.

Midazolam—Midazolam is a lipophilic drug (logP 3.9) with high protein binding (97%). Midazolam is metabolized in the liver by CYP3A4 and CYP3A5 to a hydroxylated metabolite (1-OH-midazolam) with subsequent metabolism to 1-OH-midazolam-glucuronide by UGTs. Both metabolites are pharmacologically active when 1-OH-midazolam is nearly equipotent to the parent drug.

There are no PK studies of midazolam in older children on ECMO. PK studies in neonates and young infants on ECMO show a 3-fold to 4-fold increase in Vd after initiation of ECMO for midazolam. This increase can be attributed mainly to hemodilution and sequestration of midazolam by the ECMO circuit. Mulla and colleagues⁶⁰ described a reduced Cl for midazolam, resulting in accumulation of midazolam 48 hours after initiation of ECMO in term neonates. In the study by Ahsman and colleagues,¹¹⁷ midazolam Cl in term neonates increased overtime, possibly reflecting maturation of the CYP drug-metabolizing enzymes and therefore hepatic Cl. In contrast, renal Cl of the glucuronidated active metabolite of hydroxymidazolam was decreased.¹¹⁷

In animal studies of postcardiac arrest, hypothermia midazolam Vd and Cl are decreased.^{146,147} In healthy adult volunteers, midazolam Cl but not Vd was affected by

induced mild hypothermia.¹¹³ In an adult population with traumatic brain injury with mild hypothermia (32–34°C), midazolam concentrations increased 5-fold during hypothermia, with a subsequent decrease in plasma levels during rewarming. PK evaluation showed a 2-fold increase in Vd with a more than 100-fold decrease in Cl during the hypothermic phase.¹¹⁴ During the hypothermic phase of CPB, midazolam plasma levels increase in pediatric patients.¹¹⁵

Initiation of ECMO greatly increases Vd by hemodilution and drug adsorption to the circuit. Although the effects of hypothermia on Vd remain contradictory, it seems that these changes are small compared with the effect of adsorption to the ECMO system. An initial reduction of plasma concentrations should be expected. Reduced Cl during ECMO and hypothermia greatly increases risk of adverse effects, and efforts should be made to reduce midazolam infusions when possible based on clear treatment protocols. During slow rewarming, increased Cl lowers plasma levels, necessitating increased midazolam infusions when discomfort is noted.

Fentanyl—Fentanyl is a lipophilic drug (logP 4) with a high hepatic extraction ratio. Fentanyl is sequestered to a high degree by the ECMO circuit.⁷⁷ Koren and colleagues⁸¹ reported drug sequestration of fentanyl in ECMO circuits, with a subsequent need for high fentanyl infusion rates. High fentanyl infusion rates have been reported by others as well, indicating altered PK or PD in these patients, but clear PK data in neonates and children on ECMO are lacking.^{110,148}

Animal studies have shown increased fentanyl plasma levels in hypothermia models mostly caused by reduced hepatic blood flow and a reduction of CYP3A enzyme function.^{119,120} During deep hypothermia (18–25°C), Cl seems to be greatly reduced.¹¹⁹ Several studies show an initial decrease of fentanyl plasma concentrations during CPB caused by increased Vd by hemodilution and drug sequestration to the CPB circuit components. Plasma concentrations remain stable during hypothermic CPB, indicating reduced Cl.^{121–123}

The high adsorption rate of fentanyl in ECMO circuits may necessitate high doses. Changes in ECMO circuits with reduced capacity to adsorb drugs probably reduce fentanyl needs. Reduced Cl during hypothermia with subsequent increased Cl during rewarming requires careful monitoring of patients. Rapid reduction of plasma levels may lead to agitation or opioid withdrawal symptoms.

Morphine—Morphine has a low protein binding and is metabolized by the liver to active metabolites morphine-6-glucuronide by the enzyme UGT2B7 and morphine-3-glucuronide by UGT2B7 and the enzyme-family UGT1A.

Morphine is widely used in neonatal intensive care as an analgesic and sedative during mechanical ventilation and ECMO. In 1994, Dagan and colleagues¹²⁷ reported decreased morphine Cl in neonates on ECMO, with a concomitant 2-fold increase after decannulation. Geiduschek and colleagues⁶² found a similar change in Cl of morphine in 11 newborns on ECMO. Almost half of the patients showed increased Cl over time, possibly reflecting age-related maturation of drug-metabolizing enzyme activity. However, Geiduschek and

colleagues found no significant decrease of morphine levels directly after cannulation. These investigators concluded therefore that PK of morphine was not significantly altered during ECMO.

In 2006, Peters and colleagues reported a 2-fold increase of Vd for morphine in neonates on ECMO compared with postoperative patients not treated with ECMO. Furthermore, Cl was decreased at the start of ECMO but increased over time, with normal Cl for age at day 14. The Cl of morphine-3-glucoronide and morphine-6-glucoronide is related to creatinine Cl.^{61,128}

Bansinath and colleagues¹²⁶ and Alcaraz and colleagues¹⁴⁹ found decreased Vd and total body Cl in a dog model of moderate hypothermia (30°C). In a neonatal trial assessing whole-body therapeutic hypothermia in postasphyxiated neonates, significantly higher morphine plasma levels were found in the hypothermic treatment group.¹²⁴ Apart from these changes in PK, there is evidence that morphine affinity for the μ opioid receptor is reduced by hypothermia.^{125,150}

The increased Vd found in ECMO patients is partly caused by dilution. Morphine sequestration is substantially less compared with more lipophilic drugs such as fentanyl and midazolam, explaining in part the reduced effect on Vd. Altered Cl may reflect severity of disease more than specific ECMO-related changes. The use of hypothermia in ECMO patients probably leads to higher than expected plasma levels, with a subsequent decrease in plasma levels during the rewarming phase.

Propofol—Propofol is a highly protein-bound (95%–99%) and highly lipophilic drug (logP 3.8). It is mainly metabolized in the liver by glucuronidation at the C₁-hydroxyl end. Hydroxylation of the benzene ring to 4-hydroxypropofol may also occur via CYP2B6 and 2C9. In children, propofol is not used for long-term sedation because of the possible occurrence of propofol infusion syndrome.^{151,152}

There are no in vivo data on propofol during ECMO in either the pediatric or adult population. In vitro studies show high adsorption rates by ECMO systems.^{78,80} This situation most likely results in increased Vd when used in ECMO patients. Propofol concentrations were lower than expected in a pediatric CPB population.¹³⁶ In adults, propofol concentrations decrease by 30% to 67% during CPB.^{116,153,154} There are indications that propofol PK or PD is affected by hypothermia. When using bispectral index to titrate propofol dosing on CPB, mild hypothermia reduces propofol requirements almost 2-fold in adults.^{154,155}

In pediatric ECMO patients, higher doses of propofol bolus injections are probably caused by the increased Vd caused by hemodilution and drug adsorption to the ECMO circuit components. When used as a continuous infusion during hypothermia, increased plasma levels may occur.

Neuromuscular Blocking Agents

Neuromuscular blocking agents are used during hypothermia to prevent shivering. There are no PK data on neuromuscular blocking agents in children on ECMO. Several agents have been studied during CPB. Miller and colleagues¹⁵⁶ found a decreased Vd by 40% with stable Cl for pancuronium during mild hypothermia in cats.¹⁴⁰ Vecuronium Cl during hypothermia is unaltered in rats but seems to be decreased in human adults.¹⁴³ Lower plasma levels with decreased Cl during mild and deep hypothermia are found in children on CPB. Overall, vecuronium requirements were greatly reduced during hypothermia as a result of altered PD.¹⁴⁴ Cisatracurium PK does not seem to be greatly altered in infants on mild hypothermic CPB, although dose requirements decrease during hypothermia.^{139,157}

Overall, there is evidence that PK, and especially PD, of neuromuscular blocking agents is altered during hypothermia. How PK is altered during ECMO is unknown and drugs should be titrated to effect.

Antimicrobial Drugs

Antibiotic use in ECMO patients is high, with a reported 71% use of antibiotic prophylaxis and 40% prolonged antibiotic use during ECMO. Infection rates in the pediatric ECMO population vary between 9% and 14%.^{16,158} Nosocomial or ongoing infections remain a significant problem and are associated with increased mortality.¹⁵⁸

PK data on antibiotics on ECMO are limited; only vancomycin, gentamicin, and cefotaxime have been studied in detail.

Sequestration of antimicrobial drugs by the ECMO circuit is less pronounced compared with more lipophilic drugs.

Most antibiotics are excreted via the kidney. Addition of hemofiltration potentially increases Cl for drugs with a high unbound fraction.

Efficacy of antibiotics the effectiveness of which depends on peak concentrations (such as aminoglycosides) may be reduced by increased Vd. The risk of adverse events related to high trough levels may be increased because of reduced Cl. Antibiotics the effectiveness of which depends on time greater than minimal inhibitory concentration (MIC) (such as cephalosporins and vancomycin) may be affected by differences in drug Cl as well as Vd. Both undertreatment and toxicity need to be considered when dosing antibiotics on ECMO.

To guide antibiotic dosing regimens in ECMO patients, PK models that take into account ECMO-related PK changes need to be developed.

Gentamicin—Gentamicin is an aminoglycoside antibiotic with high water solubility (logP -3) and low protein binding (0%–30%). It is mainly eliminated unchanged via the kidneys.

Five studies examined gentamicin in infants on ECMO. All found an increased Vd, ranging from 0.51 L/kg⁶⁷ to 0.748 L/kg^{63–66} compared with 0.45 L/kg in post-ECMO patients and critically non-ECMO patients.^{65,66} Cl on ECMO was decreased compared with the Cl in the post-ECMO period.^{65,66} It is unclear whether this decrease is because of ECMO itself or

because of improvement in the clinical condition. When compared with term septic neonates, gentamicin Cl on ECMO seems to be unaffected or slightly decreased.^{63–67,159} All studies showed an increased elimination half-life of 10 hours compared with 5 to 6 hours in non-ECMO patients.¹⁶⁰

Different dosing regimens were used in the studies. None reflect the current dose recommendations.

Induced hypothermia to 29°C was associated with decreased Vd and Cl in pigs.¹⁰³ However, mild hypothermia of 35°C did not affect PK in juvenile pigs.¹⁰⁴ Liu and colleagues¹⁰⁵ confirmed these latter findings in 55 neonates cooled to 34°C after asphyxia.

During CPB and deep hypothermia (18–25°C), gentamicin Vd increased 2-fold, whereas Cl decreased. It is unclear if these effects reflect the influence of hypothermia or CPB. The increased Vd reflects the findings in infants on ECMO and can mostly be contributed to dilution. The possible decrease in peak concentrations with prolonged elimination necessitates the use of therapeutic drug monitoring (TDM) for these patients, especially during hypothermia or renal replacement therapy, in which serum creatinine does not accurately reflect renal function. The kinetically guided maintenance dosing of gentamicin based on plasma concentration after the first dose should be optimized despite high interindividual PK parameter variability, especially in neonates treated for perinatal asphyxia with therapeutic hypothermia and multiorgan dysfunction syndrome.¹⁶¹

Vancomycin—Vancomycin is a glycopeptide with a high water solubility (logP -3.1) and moderate protein binding (55%). This drug exerts a high renal Cl by glomerular filtration.

Vd is either increased or unaffected by ECMO. Cl was decreased, but primarily correlated to renal function.^{68–71} There are no trials assessing the effect of hypothermia on vancomycin Cl. A decrease in renal perfusion likely results in a decreased vancomycin Cl. Especially in patients who have had a cardiac arrest with a high risk of acute renal injury, this decrease could lead to toxic plasma levels. In children on CPB, vancomycin plasma levels decrease by 45% on initiation of CPB. Overall Vd and Cl do not seem to be greatly affected.¹⁰⁹

Based on the available literature, vancomycin dosing intervals should be based on age and renal function. Drug monitoring should be used to adjust dosing.

Cephalosporins

Cefotaxime, cefuroxime, cefazolin: Cephalosporins are widely used in pediatric patients, including those on ECMO. PK of cefotaxime during ECMO and of cefuroxime during CPB is altered but plasma levels are more than the MIC using normal dosing regimens.^{101,102} Cefotaxime Cl was found to be increased during ECMO compared with the pre-ECMO and post-ECMO period, possibly reflecting improved hepatic or renal perfusion during ECMO or Cl via hemofiltration.¹⁰¹ A possible decrease in Cl caused by hypothermia increases plasma levels, negating the effects of ECMO. Cefazolin plasma levels remained greater than MIC in infants during CPB after bolus infusions before the start of bypass.¹⁰⁰ Because of the large therapeutic window of cefotaxime, the chance of reaching toxic effects is small. For

cefotaxime and cefazolin, dose adjustments do not seem to be necessary during ECMO and hypothermia.

Oseltamivir—In the recent H1N1 influenza pandemic, ECMO support was successfully initiated in children and adults, with survival rates of 70%.^{162–164} Oseltamivir is the drug of choice in H1N1 influenza, whereas alternatives such as inhaled zanamivir or intravenous zanamivir have not been evaluated in critically ill children. A case report describing 3 patients with H1N1 influenza supported with ECMO showed that adequate oseltamivir plasma levels were achieved in 2 of 3 patients. More specifically, a 2-fold dose increase of 4 mg/kg/d (vs 2 mg/kg/d) resulted in a 2-fold increase in plasma levels. The influence of the ECMO circuit seems to be limited in this small case series. One patient with profuse gastric retentions and hematemesis failed to achieve adequate plasma concentrations of oseltamivir and oseltamivir carboxylate, probably reflecting insufficient intestinal absorption of the parent drug.¹⁰⁶

Oseltamivir is metabolized in the liver by esterases. Bioavailability is about 75% after oral administration. There are indications that oral absorption of some drugs may be reduced during hypothermia in animal studies.¹⁶⁵ The active metabolite oseltamivir carboxylate is eliminated by the kidney. Hypothermia could influence bioavailability and elimination of oseltamivir and oseltamivir carboxylate. There is no evidence to alter the standard dosing regimen in hypothermic ECMO patients.

Miscellaneous

Heparin—Coagulation is affected by hypothermia. Enzymatic reactions in the coagulation cascade are decreased, resulting in prolonged activated partial thromboplastin time (aPTT) and prothrombin time.^{166,167} Platelet activation and aggregation are influenced by hypothermia. Some experimental studies show decreased platelet function and aggregation,^{168–170} whereas others show increased platelet aggregation during mild and moderate hypothermia in adults.^{171,172} Ramaker and colleagues¹⁷³ found increased clotting times with normal or enhanced thrombus strength using thromboelastography.

ECMO activates the coagulation cascade, resulting in consumption and activation of clotting factors. This situation leads to clotting factor deficiencies, impaired platelet function, thrombocytopenia, and fibrinolysis.¹⁷⁴

All ECMO patients receive heparin to reduce the risk of thromboembolic complications. Heparin infusions are titrated to either activated clotting time, aPTT, or antifactor Xa. Heparin CI is increased during ECMO by adsorption of heparin by the ECMO circuit. Higher heparin doses on ECMO are necessary to maintain anticoagulation.^{175,176}

Anticoagulation targets may be different during therapeutic hypothermia on ECMO. Careful monitoring using multiple tests helps to titrate heparin infusions in these patients.

Phenobarbital—Phenobarbital is a long-acting barbiturate mainly eliminated via the liver by CYP 2C19. It is partly bound to protein (20%–45%) with a logP of 1.47. Phenobarbital PK data during ECMO are limited to a single case report. A slightly Vd (1.2 L/kg) with a

normal serum elimination half-life (92 hours) resulted in low but still therapeutic serum concentrations. Dose recommendations cannot be made based on this single case report, but clinicians should be aware that higher loading doses may be required.¹²⁹ In hypothermic children, Cl and Vd of pentobarbital and phenobarbital seem to be reduced.^{130,133}

Filippi and colleagues¹⁷⁷ described increased plasma levels of phenobarbital with decreased Cl in neonates treated for perinatal asphyxia with therapeutic hypothermia. Barbiturates are primarily metabolized in the liver by the hepatic microsomal enzyme system. The metabolites are excreted in the urine and, less commonly, in the feces. Reduction of enzymatic processes and redistribution of blood flow influence PK, possibly negating the decreased plasma levels reported during ECMO. TDM is advised in these patients to monitor plasma levels during cooling and rewarming to prevent toxicity and withdrawal.

SUMMARY

Almost 10% of all pediatric ECMO runs occur during or shortly after CPR. With the increased use of therapeutic hypothermia, most of these patients are cooled during their ECMO run. Evidence-based dose regimens are still lacking for many regularly used drugs in children on ECMO, either with or without hypothermia. Our understanding of PK changes is insufficient to prepare a predictive model. The combination of routine sparse sampling, drug assay via LC-MS, and a PK analysis using NONMEM in combination with validated PD end points such as the COMFORT behavioral scale¹⁷⁸ or face, legs, arms, cry, consolability (FLACC)¹⁷⁹ and a numeric rating scale to assess discomfort and pain allow the study of drug behavior in these vulnerable patients without harm to the individual.

Overall, Vd changes occur rapidly at start of ECMO as a result of hemodilution and adsorption of drugs by the ECMO system. Initial changes in Vd may necessitate higher doses to achieve adequate plasma concentrations. If Vd is increased and stays unchanged, steady state levels are affected only by the dose rate and Cl rate.

Changes in PK are drug and circuit dependent, with more dramatic changes found with lipophilic drugs and silicone oxygenators. Differences in ECMO circuits used, patient populations, and diseases may influence PK and PD further. Changes in Vd as a result of hypothermia are difficult to predict during ECMO, but seem to be small compared with the changes caused by adsorption of drugs to the ECMO circuit. Cl may be more dramatically changed by combining ECMO with therapeutic hypothermia. Both organ perfusion and enzymatic reactions are reduced by hypothermia. Most data on PK of drugs during hypothermia show decreased Cl with higher plasma levels. Particularly during rewarming, clinicians need to be vigilant and expect rapid decreases in plasma levels of most sedatives.

The greatest changes are:

- Increased Vd, especially for lipophilic drugs on initiation of ECMO
- Decreased Cl as a result of ECMO and hypothermia, especially of drugs dependent on enzymatic reactions

- Reduced renal Cl as a result of reduced renal perfusion during ECMO and hypothermia for drugs cleared by glomerular filtration

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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.

Table 1

Overall effect on PK by different treatment modalities

		ECMO	CPB	Hypothermia
Absorption	Gastrointestinal tract	?	?	↓
Vd		↑	↑	—/↓
	Extracellular water	↑	↑	↑↓
	Drug adsorption	↑	↑	?
	Blood volume	↓	↓	↓
	Protein binding	?	?	↓
	Ionization	?	?	↑
Cl		↓	↓	↓
	Organ perfusion	?	↓	↓
	Kidney	?	↓	↓
	Liver	?	↓	↓
	Enzymatic Cl	↓	↓	↓
	Receptor	?	?	↓

Abbreviations: ↓, decreased; ↑, increased; ?, unknown.

Table 2

Changes of PK for different drugs in different treatment modalities

Drugs	ECMO	Hypothermia	CPB
Cardiovascular Drugs			
Amiodarone	Increased dose ⁹⁰		
Bumetanide	Vd ↑ ⁷⁴		
Esmolol	Increased dose ⁹¹		
Furosemide	No change ⁹²		
Nesiritide	Increased dose ⁹³		
Nicardipine	Vd-, Cl- ^{94,95}		
Prostaglandin E ₁	Increased dose ⁹⁶		
Sildenafil	Vd ↑, Cl ↑ ⁹⁷		
Antimicrobial Drugs			
Caspofungin	No change ⁹⁸		
Caspofungin	Low plasma levels ⁹⁹		
Cefazolin			Vd ↑, Cl ↓ ¹⁰⁰
Cefotaxime	Vd ↑, Cl- ¹⁰¹		
Cefuroxime			No change ¹⁰²
Gentamicin	Vd ↑, Cl ↓ ⁶³⁻⁶⁷	Cl ↓ ¹⁰³⁻¹⁰⁵	Vd ↑ ¹⁰⁰
Oseltamivir	Vd-, CL- ¹⁰⁶		
Ribavirin	Vd ↑ ¹⁰⁷		
Ticarcillin-clavulanic acid	No change ¹⁰⁸		
Vancomycin	Vd ↑, Cl ↓ ^{69,70}		No change ¹⁰⁹
Vancomycin	No change ⁶⁸		
Voriconazole	Vd ↑, Cl ↓ ^{98,99,111}		
Neurological Drugs			
Midazolam	Vd ↑, Cl ↓ ^{60,112}	Cl ↓, Vd ↑ ^{113,114}	Vd ↑, Cl ↓ ^{115,116}
Midazolam	Vd ↑, Cl ↑ ^{117,118}		
Fentanyl	High doses ¹¹⁰	Cl ↓, Vd ↓ ^{119,120}	Vd ↓, Cl ↓ ¹²¹⁻¹²³
Morphine	No change ⁶²	Cl ↓, ¹²⁴ Vd ↓ ¹²⁶	
Morphine	Vd ↑, Cl ↓ ^{61,127,128}		
Phenobarbital	Vd ↑ ¹²⁹	Cl ↓ ¹³⁰	
Phenytoin		Cl ↓, Vd- ^{131,132}	
Pentobarbital		Vd ↓, ¹³³ Cl ↓ ¹³⁴	
Propofol		Cl ↓ ¹³⁵	V ↑, Cl- ^{116,136} Cl ↑ ¹³⁷
Topiramate		Cl ↓ ¹³⁸	
Neuromuscular Blocking Drugs			
Cisatracurium			Cl-, Cl ↓ ¹³⁹

Drugs	ECMO	Hypothermia	CPB
Pancuronium		Vd ↓, Cl ↓ ¹⁴⁰	Vd ↑, Cl ↓ ^{141,142}
Vecuronium		Cl ↓ ¹⁴³	Cl ↓ ¹⁴⁴
Miscellaneous			
Ranitidine	Vd ↑, Cl ↓ ⁷²		
Theophylline	Vd ↑, Cl ↓ ⁷³	Vd↓ ¹⁰³	