Evaluation of Altered Drug Pharmacokinetics in Critically Ill Adults Receiving Extracorporeal Membrane Oxygenation

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Extracorporeal membrane oxygenation (ECMO) is a life-support modality used in patients with refractory cardiac and/or respiratory failure. A significant resurgence in the use ECMO has been seen in recent years as a result of substantial improvements in technology and survival benefit. With expanding ECMO use, a better understanding of how ECMO affects drug pharmacokinetics (PK) is necessary. The vast majority of PK studies in patients receiving ECMO have been conducted within neonatal or pediatric populations or within a controlled environment (e.g., in vitro or ex vivo). Because of significant differences in absorption, distribution, metabolism, and excretion, it may be inappropriate to extrapolate these PK data to adults. Thus, the aims of this review are to evaluate the changes in drug PK during ECMO and to summarize the available PK data for common drugs used in the adult critically ill patients during ECMO support. A search of the PubMed (1965–July 2016), EMBASE (1965–July 2016), and Cochrane Controlled Trial Register databases was performed. All relevant studies describing PK alterations during ECMO in ex vivo experiments and in adults were included. Evaluation of the data indicated that drug PK in adults receiving ECMO support may be significantly altered. Factors influencing these alterations are numerous and have intricate relationships with each other but can generally be classified as ECMO circuit factors, drug factors, and patient factors. Commonly used drugs in these patients include antimicrobials, sedatives, and analgesics. PK data for most of these drugs are generally lacking; however, recent research efforts in this patient population have provided some limited guidance in drug dosing. With an improved understanding of altered drug PK secondary to ECMO therapy, optimization of pharmacotherapy within this critically ill population continues to move forward.

Key Words extracorporeal membrane oxygenation, pharmacokinetics, hypnotics and sedatives, analgesia, antibacterial agents.

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Extracorporeal membrane oxygenation (ECMO) is a life-support modality used in patients with refractory cardiac and/or respiratory failure. A significant resurgence in the use ECMO has been seen in recent years as a result of substantial improvements in technology and survival benefit demonstrated in the Conventional Ventilator Support versus Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Failure (CESAR) trial.[1] According to the Extracorporeal Life Support Organization (ELSO) registry, ECMO has been used in more than 22,000 adult patients worldwide since 1990.[2]

With expanding ECMO use, a better understanding of how ECMO affects drug pharmacokinetics (PK) is necessary. Patients receiving

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ECMO often receive sedatives, analgesics, antibiotics, and other drugs for their underlying conditions or concomitant disease states. Several studies have demonstrated altered PK profiles for commonly used drugs in these patients.[3, 4] Because of these alterations, effective dosing of antimicrobials, sedatives, and analgesics remains a significant challenge. The failure to appropriately dose medications may lead to inappropriate drug serum concentrations and clinical failure or toxicities.

In previous decades, the vast majority of PK studies in patients receiving ECMO were conducted within neonatal or pediatric populations or within a controlled environment (e.g., in vitro or ex vivo). As a result of significant differences in absorption, distribution, metabolism, and excretion, it may be inappropriate to extrapolate these PK data to adults. Fortunately, during the past decade, an increase in the number of studies evaluating drug PK in the adult ECMO population has been observed. This review aims to highlight factors that may alter PK profiles of drugs as well as review a selection of drugs frequently encountered in adult patients receiving ECMO.

Literature Search

A search of the PubMed (1965–July 2016), EMBASE (1965–July 2016), and Cochrane-Controlled Trial Register databases was performed to provide data for this review. Search terms included *pharmacokinetics, extracorporeal membrane oxygenation, critical illness, hypnotics and sedatives, analgesia,* and *antibacterial agents*. Variations of these search terms were also used. Studies in languages other than English were excluded. A manual review of references from retrieved articles was also performed. All relevant studies describing PK alterations during ECMO in ex vivo experiments and in adults were included.

ECMO Basics

ECMO is a form of life support that provides temporizing measures for patients with refractory cardiorespiratory failure. Depending on the configuration of the ECMO circuit, respiratory support or a combination of cardiac and respiratory support can be provided. Patients with an underlying respiratory process (hypercapnia, hypoxemia) without compromised cardiac output can use venovenous (VV) ECMO support. Patients with cardiac and/or respiratory failure with hemodynamic compromise, severely diminished cardiac output, or severe right heart failure require venoarterial (VA) ECMO support. Current ELSO guidelines provide recommendations on indications and contraindications for ECMO support.[5]

The cannulation strategy used determines the type of support that is provided by the ECMO circuit. Both VV ECMO and VA ECMO remove blood from the venous circulation via intake cannula. The difference is the site of the outflow cannula. In VV ECMO, the circuit is connected in series with the heart and lungs, and oxygenated blood is returned to the venous circulation. Adequate right heart function is required to circulate the newly oxygenated blood through the systemic circulation. Therefore, VV ECMO provides only respiratory support. In contrast, VA ECMO is connected in parallel with the heart and lungs. Oxygenated blood is returned to the arterial circulation. Adequate right heart function is not required for the oxygenated blood to reach the systemic circulation. Therefore, VA ECMO provides both cardiac and respiratory support.[6]

The ECMO circuit is composed of multiple components: the blood pump, membrane oxygenator, conduit tubing, anticoagulation, and other miscellaneous components (Figure 1). The blood pump is responsible for circulating blood through the circuit, and, in general, the blood flow rate determines the degree of support that the circuit provides to the patient.

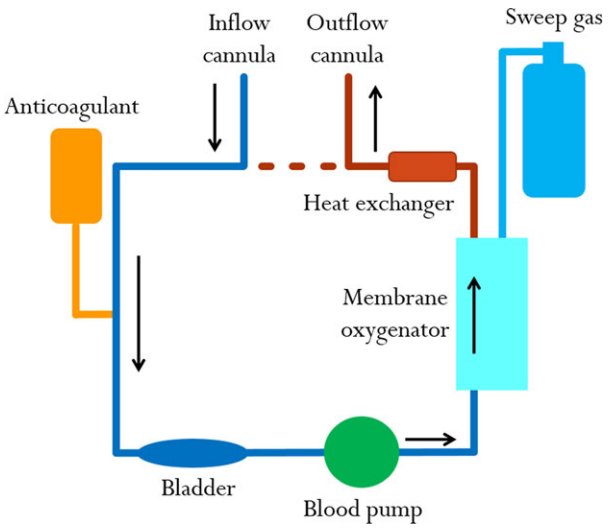

Figure 1. Extracorporeal membrane oxygenation circuit and its components.

The membrane oxygenator is responsible for oxygenating the blood and removing carbon dioxide. There are a variety of different membrane materials.[5] Sweep gas is composed of 100% oxygen or a mix of oxygen and carbon dioxide and flows across the membrane surface opposite of the blood compartment, providing a source of oxygen and removing carbon dioxide. A flexible bladder in series with the blood pump helps to ensure adequate blood flow and pressure within the circuit and reduce the risk of an air embolism.

Circuit tubing is primarily composed of polyvinyl chloride and is available in unmodified and modified types. Modified types, including those with covalently bonded heparin, were developed to reduce circuit thrombosis. Before initiating ECMO flow, the conduit tubing is typically primed with crystalloid but may be "pre-primed" with albumin. For infants, packed red blood cells are used to bring the hematocrit to 30–40% as a result of the risk of hemodilution.[5]

To ensure that thrombus development does not occur in the oxygenator and possibly the circuit, patients receiving ECMO should be anticoagulated. The most commonly used anticoagulant is unfractionated heparin, but alternatives include direct thrombin inhibitors such as argatroban and bivalirudin.[7] Dosing strategies may differ between centers, but generally full systemic dosing is used. Other miscellaneous components include a heat exchanger to warm the blood before return to the patient as well as a variety of monitors and alarms.

Alterations in Drug PK Profiles

There is a wide range of factors that influence the PK of drugs during ECMO support. Understanding these factors is essential to better evaluate potential PK changes and derive approaches to dosing. Although these factors are numerous and have complex relationships, they can generally be divided into circuit, drug, and patient factors (Figure 2).

Circuit and Drug Factors

The ECMO circuit is a complex device that can alter drug PK as a result of an intricate interaction between the ECMO circuit and physiochemical properties of the individual drugs. The ECMO circuit can be considered an additional PK compartment as a result of its effects on volume of distribution (Vd), drug distribution, and drug clearance. Recognizing this additional compartment is critical when evaluating drug PK in clinical applications.

Drug Sequestration: Circuit Factors

Drug sequestration in ECMO circuits is a known phenomenon, but few studies have evaluated the propensity of drugs to be affected

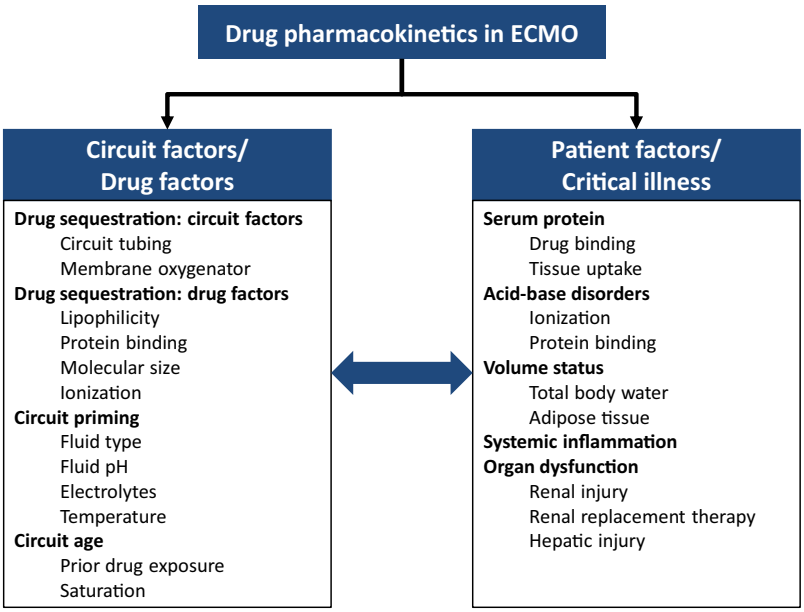

Figure 2. Factors influencing drug pharmacokinetics in patients receiving extracorporeal membrane oxygenation (ECMO).

within the adult population. ECMO circuits have large surface areas as a result of the membrane oxygenator, conduit tubing, and other circuit components.[8] Therefore, drugs have the potential to bind to these surfaces over time, resulting in an increase in the Vd and subsequent decreases in their serum concentrations and clearance.

Drug sequestration is influenced by several factors, including the design of the oxygenator, conduit tubing, individual drug properties, and composition of the priming solution. Oxygenators are available in different types, such as silicone rubber, polymethylpentene, microporous hollow fiber, or solid hollow fiber. Conduit tubing is primarily composed of polyvinyl chloride and is available in unmodified and modified types.[8] Data comparing unmodified and modified conduit tubing are lacking.[9] In an ex vivo study, modified tubing was shown to sequester 35–58% of morphine and 30–40% of fentanyl.[9] Oxygenators provide a large surface area for sequestration, but current data suggest that oxygenators contribute minimally to drug loss compared with conduit tubing.[10–12] One ex vivo study compared losses of fentanyl and morphine in ECMO circuits with and without an oxygenator.[13] The average fentanyl adsorption was 80% in circuits without oxygenators and 83–86% in circuits with different oxygenator types. Similarly, the average morphine adsorption was 40% in all circuits with or without oxygenators.

Drug Sequestration: Drug Factors

A variety of drug physiochemical properties may interplay with drug sequestration, as not all drugs have the same propensity for binding. Two properties that studies have shown to affect drug sequestration to the greatest degree are lipophilicity and protein binding. Other properties such as molecular size and ionization are theorized to also play a role, but insufficient data are available to characterize their potential effects.

The lipophilicity of a compound is normally indicated by the octanol/water partition coefficient (logP). A higher positive value indicates increased lipophilicity, whereas a negative value indicates increased hydrophilicity. Lipophilic drugs have consistently shown a greater propensity for drug sequestration compared with hydrophilic drugs, in part because of higher solubility in organic components of the circuit. An ex vivo study was conducted using ECMO circuits through which whole blood was circulated, and a number of drugs were tested for sequestration.[14] On average, 96% of fentanyl and 87% of midazolam were lost to the circuit at 24 hours. In contrast, no significant loss of morphine was observed. Fentanyl and midazolam have a logP of 4.05 and 3.89, respectively. In contrast, morphine has a logP of 0.89.[14] Therefore, the difference in sequestration between fentanyl and midazolam compared with morphine is likely secondary to differences in lipophilicity. These findings were validated by demonstrating that drug loss is associated with logP values, with more lipophilic drugs having higher losses.[15]

Protein binding is another significant influencer of drug sequestration within the circuit. An ex vivo study compared the loss of drugs with varying degrees of protein binding circulating in closed ECMO circuits.[16] Drugs with higher protein binding were found to have higher losses despite similar lipophilicity. For instance, both ciprofloxacin and thiopentone have a logP of 2.3, but ciprofloxacin is 20–40% protein bound whereas thiopentone is 80% protein bound. Mean losses were 4% and 88%, respectively. In a linear regression model, both logP and protein binding were highly significant predictors of drug loss in the circuit.[16]

A complicating factor related to drug sequestration is a potential redistribution phenomenon secondary to this additional PK compartment.[8] Sequestrated drug may continue to be released from the circuit surface after the cessation of drug administration, resulting in an extended duration of effect. This prolonged pharmacologic activity may be unwelcome, especially with regard to sedative and analgesic drugs when trying to wean patients off of ECMO.

Circuit Priming

Circuit priming may have a significant impact on drug PK through increasing the effective circulating volume of the patient. Factors include the type of priming fluid, added electrolytes, pH, and temperature. Collectively, these factors may affect the degree of sequestration within the circuit, but limited data exist to characterize these interactions.[17] It is unclear what effect different priming fluids may have on drug PK. Ex vivo ECMO circuits primed with either crystalloid or whole blood through which various drugs were circulated were compared.[18] In crystalloid-primed circuits, 72% of ampicillin, 17.6% of

fosphenytoin, and 87% of fentanyl were lost. In comparison, in blood-primed circuits, 15% of ampicillin, 31% of fosphenytoin, and 100% of fentanyl were lost. Other evaluated drugs exhibited widely varying losses. Although the specific values may be somewhat trivial, it is important to understand the potential ramifications, as these differences may lead to therapeutic failure or toxicity.

Circuit Age

The age and type of circuit may influence the degree of drug loss.[3, 12, 19] One group[19] studied the losses of various drugs in closed ECMO circuits: one new and one used clinically by a patient. Phenobarbital was shown to have higher losses observed in the new circuit compared with the used circuit. Other studied drugs, including vancomycin, gentamicin, and phenytoin, followed similar patterns. The authors also noted that steady-state concentrations of morphine significantly fell (from 68.2 to 11.6 ng/ml) after changing the oxygenator, suggesting that older circuits may cause less sequestration as a result of prior saturation, and changing oxygenators may require an increase in drug dosing to compensate. A recent study demonstrated that polypropylene hollow-fiber membrane oxygenators with centrifugal pumps had significantly higher fentanyl and midazolam recovery compared with silicone membrane oxygenators with roller pumps.[15] No differences between freshly primed ECMO circuits and clinically used ECMO circuits (previously exposed to morphine, midazolam, amoxicillin, cefotaxime, hydrocortisone, and vancomycin for > 48 hrs) after 3 hours were noted.

Patient Factors

Critically ill patients are prone to significantly reduced serum protein levels compared with healthy adults, and PK alterations have been described in detail elsewhere.[20–23] Reduced serum protein levels result in increased free fractions of protein-bound drugs and may alter drug clearance and uptake into the tissues. Significant alterations in serum pH may also have an effect on protein binding.[16]

Critically ill patients often have volume status derangements, which may affect drug Vd.[20–22] The true impact of ECMO on Vd in adults is difficult to quantify, as most PK analyses were performed in neonates.[24] Compared with adults, newborns have higher proportions of total body water and lower proportions of adipose tissue, leading to higher Vd of hydrophilic drugs and lower Vd of lipophilic drugs.[8, 21] Development of organ dysfunction and systemic inflammation may contribute to an increase in Vd and decrease in clearance.[21, 22] Obese patients have increased adipose tissue, providing sites for sequestration of lipophilic drugs. Regardless of which population, it is expected that drugs with lower Vd would have significant alterations in Vd as a result of a greater relative increase compared with drugs with larger Vd.

Organ dysfunction is common in patients receiving ECMO support. These patients are especially prone to renal injury and reduction in drug clearance.[25] In addition, nonpulsatile circulation in VA ECMO causes altered tissue perfusion, decreased glomerular filtration, and upregulation of the renin-angiotensin system.[26] Patients may require renal replacement therapy, which is a major consideration when dosing drugs.[23] Hepatic injury is common and results in the decreased metabolism of many drugs.[15]

Impact on Antimicrobials

By understanding the PK alterations in patients receiving ECMO, clinicians are better equipped to make informed decisions regarding dosing of antimicrobials (Table 1). By optimizing dosing, therapeutic failure and toxicity may be minimized while potential emergence of resistant microorganisms may also be avoided or reduced. The importance of variation in antimicrobial PK cannot be underestimated, and the risks versus benefits of dosage adjustments should be carefully considered.

H1N1 Influenza Pandemic and Oseltamivir

The 2009 and 2010 H1N1 influenza pandemic serves as an excellent reminder of the importance of optimal antimicrobial dosing in patients receiving ECMO. During this pandemic, there was a significant increase in the incidence of acute respiratory distress syndrome (ARDS) requiring ECMO support. Oseltamivir emerged as the preferred therapy, with the World Health Organization[48] recommending doses up to 150 mg twice/day—double the standard adult dose. This recommendation was largely empiric with little PK data to support the use of higher doses, and ECMO's effects on this drug were largely unknown.

Table 1. Physiochemical Properties, Pharmacokinetic Changes, and Dosage Adjustments for Select Drugs

Drug Class	Medication	Protein Binding[27]	Octanol/ Water Partition Coefficient[27]	Volume of Distribution[27]	Expected Effect	Actual Effect	Dosage Adjustment
Beta-Lactams	Ampicillin[18]	15–28%	0.67	20–27 L	Minimal to moderate sequestration Large increase in Vd	Crystalloid-primed circuit: 72% loss in circuit Blood-primed circuit: 15% loss in circuit	Consider alternative agents
	Cefazolin[18]	74–86%	–0.58	35 L[a]	Moderate sequestration Large increase in Vd	22% loss in both crystalloid- and blood-primed circuits	May be required
	Ceftriaxone[13]	85–95%	–0.01	5.78–13.5 L	Moderate sequestration Large increase in Vd	20% loss in circuit	Not required
	Meropenem[28, 29]	2%	–0.69	15–20 L	Minimal sequestration Large increase in Vd	No significant difference compared with matched controls	Not required
	Piperacillin-tazobactam[28]	30%	0.67	16.8 L[a]	Minimal sequestration Large increase in Vd	No significant difference compared with matched controls	Not required
Glycopeptides	Vancomycin[30]	50%	–4.4	28–70 L[a]	Minimal sequestration Large increase in Vd	No significant difference compared with matched cohort	Not required; dosing guided by therapeutic drug monitoring
Fluoroquinolones	Ciprofloxacin[16]	20–40%	2.3	147–189 L[a]	Moderate sequestration Moderate increase in Vd	No significant loss in circuit	Not required
	Levofloxacin	24–38%	0.65	88.9 L[a]	Minimal to moderate sequestration Moderate increase in Vd	Unknown, not yet studied May not require dosage adjustment	Not required
	Moxifloxacin	50%	0.01	119–189 L[a]	Minimal to moderate sequestration Moderate increase in Vd	Unknown, not yet studied May not require dosage adjustment	Not required
Aminoglycosides	Gentamicin, tobramycin, amikacin[19, 31]	< 30%	< 0.0	14–21 L[a]	Minimal sequestration Large increase in Vd	Unknown; studies performed primarily in neonates or children; offset by therapeutic drug monitoring	Insufficient data; dosing guided by therapeutic drug monitoring
Antifungals	Fluconazole[11]	12%	0.56	42 L[a]	Minimal sequestration Large increase in Vd	Unknown; studies performed primarily in neonates or children showed increased Vd and similar clearance	Insufficient data; increased loading dose may be required; maintenance doses may not require adjustment
	Voriconazole[18, 32]	58%	2.56	322 L[a]	Moderate to high sequestration Minimal increase in Vd	71% loss in circuit Time-dependent saturation of circuit	Increased loading dose required (100% increase); daily therapeutic drug monitoring recommended to monitor for circuit saturation
	Caspofungin[13, 32, 33]	97%	–2.80	8–10 L	Minimal to moderate sequestration Moderate increase in Vd	Limited and conflicting data May require dosage adjustment	Insufficient data; dosage adjustment may be required

(continued)

Table 1 (continued)

Drug Class	Medication	Protein Binding[27]	Octanol/ Water Partition Coefficient[27]	Volume of Distribution[27]	Expected Effect	Actual Effect	Dosage Adjustment
Antivirals	Oseltamivir[10, 34, 35]	42% (active carboxylate 3%)	1.16	23–26 L	Minimal to moderate sequestration Large increase in Vd	Larger Vd, C_{max}, and AUC compared with healthy references	Not required
Sedatives and analgesics	Midazolam[14, 36]	97%	3.89	70–217 L[a]	High sequestration Moderate increase in Vd	Significant drug sequestration: 97% loss at 24 hrs	Increased dose required; consider alternative agents
	Dexmedetomidine[12]	94%	3.39	118 L	Minimal to moderate sequestration Minimal increase in Vd	~40% loss in circuit at 60 min	Increased starting dose may be required
	Propofol[37, 38]	95–99%	3.79	4200 L[a]	High sequestration Minimal increase in Vd	70% loss in circuit at 45 min	Increased dose may be required; consider alternative agents
	Fentanyl[14, 36, 39–43]	79–87%	4.05	280–420 L[a]	High sequestration Minimal increase in Vd	Significant drug loss at 24 hrs	Escalating dose required; consider alternative agents
	Morphine[14, 18, 44, 45]	20–35%	0.89	70–350 L[a]	Minimal sequestration Mild to moderate increase in Vd	Minimal to moderate sequestration	May be required
	Ketamine[46, 47]	47%	2.9	140–210 L[a]	Moderate to high sequestration Minimal increase in Vd	Unknown	Insufficient data

Vd = volume of distribution; C_{max} = maximum concentration; AUC = area under the curve.
[a]Standardized to a 70-kg patient.

A single-center, prospective, population PK study examined the PK of oseltamivir and its active metabolite, oseltamivir carboxylate, in patients receiving ECMO.[34] Patients were given oseltamivir 75 mg enterally twice/day. Mean serum concentrations of oseltamivir carboxylate on day 1 did not differ significantly from concentrations on day 5, suggesting that no loading dose is necessary in patients receiving ECMO. The mean Vd was 179 L in patients receiving ECMO compared with 26 L in healthy adult references. Despite the larger Vd, a significantly higher maximum concentration (C_{max}) and area under the curve (AUC) (509 ng/ml and 4346 ng·hr/ml, respectively) were found on day 5 compared with those in the healthy adult references (335 ng/ml and 2976 ng·hr/ml, respectively) on day 7. This difference was attributed to reduced clearance in patients receiving ECMO. Another prospective PK study[10] in patients receiving continuous VV hemodialysis (CVVHD) with or without ECMO support confirmed these results. Enteral oseltamivir 150 mg twice/day was administered to four patients receiving both CVVHD and ECMO support. The median C_{max} and AUC of oseltamivir carboxylate over a 12-hour dosing interval were 981 ng/ml and 9390 ng·hour/ml, respectively. No substantial differences between preoxygenator and postoxygenator serum concentrations were found. Another small study found similar results.[35] These data indicate that a higher AUC of the active drug is achieved in patients receiving ECMO and therefore no dosage adjustment is necessary.

β-Lactams

β-Lactams are time-dependent antibiotics; therefore, understanding PK alterations in patients receiving ECMO is critical in maintaining serum levels above the minimum inhibitory concentration (MIC). Several small studies evaluated the PK of various β-lactams. Recently, a retrospective case-control study evaluating the PK of meropenem and piperacillin-tazobactam in adult patients receiving ECMO support was completed.[28] Both agents were administered as 30-minute intermittent infusions. No significant differences in PK and achievement of adequate drug levels above the MIC were found between the ECMO group and historical controls. However, both had substantially altered PK compared with healthy adult references with significantly longer half-lives and larger Vd. Therefore, the PK profiles of both drugs in patients receiving ECMO are likely reflective of critical illness rather than ECMO itself. The available data suggest that dosing strategies for critically ill adults may be used in patients receiving ECMO to achieve adequate time and level above MIC.[28, 29]

Although data are limited for other β-lactams, evaluating their physiochemical properties may give insight into potential PK alterations. β-Lactams, with the exception of the anti staphylococcal penicillins, are relatively hydrophilic, whereas protein binding varies.[27] Meropenem has a logP of −0.69 and protein binding of 2%, whereas piperacillin-tazobactam has a logP of 0.67 and protein binding of 30%. Therefore, it is reasonable to predict that these two drugs would exhibit similar PK alterations in patients receiving ECMO, which was confirmed in a study.[28] Ceftriaxone has a logP of −0.01 and protein binding of 85–95%, suggesting a potential degree of sequestration. These predictions were confirmed in one ex vivo study, which found a 20% loss within the circuit.[13]

There are limitations to using physiochemical properties to predict drug sequestration. Ampicillin has similar physiochemical properties as piperacillin-tazobactam, with a logP of 0.67 and protein binding of 15–28%.[27] It would be a reasonable to predict similar PK alterations; however, researchers[18] confirmed a 15–71% loss of ampicillin depending on the type of circuit priming fluid. Therefore, it may not always be appropriate to extrapolate drug sequestration based on physiochemical properties. Nevertheless, because PK data are lacking for many drugs, evaluation of physiochemical properties may be helpful to guide dosing strategies.

Vancomycin

Vancomycin is a glycopeptide antibiotic whose efficacy is associated with maintaining an AUC: MIC ratio of ≥ 400.[49] Few studies have examined the PK of vancomycin in patients receiving ECMO. One retrospective, matched-cohort study compared the population PK of vancomycin administered as a continuous infusion during the first 24 hours of treatment during ECMO support compared with a control cohort.[30] No significant differences were found in vancomycin levels during the first 24 hours. Comparable Vd and clearance were found between the two groups. Median AUC between both the ECMO and control cohort was also similar (628 and

698 mg·hr/L, respectively), suggesting an adequate AUC:MIC ratio for susceptible organisms.

These results contrast with those of earlier adult and neonatal PK studies, which generally found an increased Vd and decreased clearance during ECMO support.[50] There are several plausible reasons for these discrepancies. Neonates and children may be more susceptible to Vd changes as a result of their smaller total body water. In addition, modern ECMO circuits require less priming fluid and have less conduit tubing compared with circuits used in older studies, potentially resulting in a smaller increase in Vd. Current data suggest that ECMO therapy does not significantly influence vancomycin PK compared with other critically ill adults who were not receiving ECMO.[30] Consequently, vancomycin may be dosed by using a similar approach, which is eased by the availability of therapeutic drug monitoring.

Fluoroquinolones

Compared with β-lactams and vancomycin, less data are available regarding the PK of fluoroquinolones in patients receiving ECMO support. An ex vivo study using closed ECMO circuits evaluated sequestration of various drugs, including ciprofloxacin.[16] No significant loss of ciprofloxacin as a result of the ECMO circuit was found compared with controls. Considering that fluoroquinolone efficacy is associated with AUC:MIC ratio, this small loss suggests that ciprofloxacin's efficacy is minimally affected.[51]

Compared with ciprofloxacin, levofloxacin and moxifloxacin are less lipophilic and have similar protein binding.[27] It would be reasonable to expect a similar lack of drug loss as a result of the ECMO circuit. Therefore, dosage adjustments for fluoroquinolones may not be required in patients receiving ECMO. However, more robust PK data are required to make a definitive recommendation.

Aminoglycosides

Unfortunately, little data exist for the PK of aminoglycosides in adult patients receiving ECMO.

Studies examining aminoglycoside PK in patients receiving ECMO are limited to the neonatal and pediatric populations. Neonatal PK studies have demonstrated an increase in the Vd of gentamicin (from 0.43 to 0.66 L/kg), decreased clearance, and a prolonged half-life.[31] Minimal loss (≤ 10%) of gentamicin was noted in an ex vivo study with pediatric ECMO circuits.[19] It is difficult to extrapolate PK data derived from these studies to the adult population as a result of the differences between the neonatal and adult population as well as changes in ECMO technology since the publication of these studies. However, this lack of PK data may be offset by the availability of therapeutic drug monitoring.

Antifungals

Azole antifungals, like β-lactams, are time-dependent agents; therefore, achieving and maintaining adequate levels above the MIC are important. However, PK studies of azole antifungals in adult patients requiring ECMO support are lacking. Available studies for fluconazole are limited to infants and children. A PK study performed in infants younger than 120 days receiving fluconazole prophylaxis or treatment demonstrated that compared with historical controls, infants receiving ECMO had a greater median Vd but similar median clearance.[11] Preoxygenator and postoxygenator levels of fluconazole were not significantly different. No relationship was noted between fluconazole Vd and volume of exogenous blood needed to prime the circuit. As with aminoglycosides, it is difficult to extrapolate these PK data to the adult population, but higher loading doses of fluconazole may be warranted whereas standard maintenance doses may be sufficient.

Voriconazole is highly lipophilic and moderately protein bound, suggesting a high potential for sequestration within the circuit.[27] A 71% loss of voriconazole was reported in ex vivo ECMO circuits.[18] Another group[32] reported a case of voriconazole use in a patient requiring ECMO support. The patient initially received doses of 6 mg/kg every 12 hours for two doses followed by 4 mg/kg every 12 hours before the initiation of ECMO. On initiating ECMO support, the dose was increased empirically to 6 mg/kg every 12 hours. With the increased dosing, trough and peak levels were similar to pre-ECMO levels (7.45 and 10.90 μg/ml, respectively) for the first 48 hours. However, after 48 hours, trough and peak levels were significantly increased to supratherapeutic levels (13.28 and 16.71 μg/ml, respectively) requiring a reduction in dose, suggesting time-dependent saturation of the circuit. Therefore, a larger loading dose is required to achieve adequate levels, but levels should be

carefully monitored and doses decreased once saturation occurs to avoid toxicity (goal range 2–5.5 μg/ml).[52]

Limited PK data are available for the echinocandins, but a 43% caspofungin sequestration has been demonstrated in ex vivo ECMO circuits.[16] Researchers[32] reported the case of a patient receiving caspofungin 70 mg/day while receiving ECMO. No significant differences in peak concentrations or Vd were found between the patient during ECMO and adult references. Unlike the previous study, there was no demonstration of sequestration. These results are also in contrast to another case report that reported low to undetectable concentrations in a patient receiving ECMO.[33] Given that echinocandin efficacy is associated with peak concentrations, these conflicting data are of limited utility but should provide clinicians with a low threshold for escalating antifungal therapy if patients are not responding appropriately. More robust data are required to reach a conclusion regarding echinocandin dosage adjustments in patients receiving ECMO.

Impact on Sedatives and Analgesics

Sedation and analgesia should be used cautiously in critically ill patients to prevent the development of dependence and delirium. Significant emphasis has been put on limiting sedation to allow for daily neurocognitive assessments; however, strictly adhering to these recommendations may be challenging in patients receiving ECMO. Individual clinical scenarios often dictate the necessary level of sedation and analgesia necessary for patients. It is important to identify patients who may be mobile with ECMO compared with patients requiring deep sedation to prevent cannula dislodgement or to minimize oxygen consumption and optimize ventilation. Understanding the influence of ECMO on sedative and analgesic medications is key in appropriately managing these patients (Table 1). Several reports have demonstrated increasing sedative requirements in patients receiving ECMO. Most of these studies were limited to pediatric or neonatal patients, and it is unclear whether similar issues are demonstrated in adult patients.[8, 36, 39, 53, 54]

Midazolam

Midazolam has been frequently used to help maintain a deeper level of sedation in patients when clinically necessary for ECMO. Significant midazolam sequestration has been demonstrated in several neonatal studies. An ex vivo study[14] was one of the first to demonstrate sequestration in adult ECMO circuits. The authors used an ex vivo ECMO circuit to characterize drug disposition from baseline to 24 hours after addition of the medication to the ECMO circuit. Control samples were used to ensure that changes in concentration over time were the result of drug disposition and not the result of normal drug elimination PK. Values for midazolam recovery from the ECMO circuit and the controls at 24 hours relative to baseline were 13% and 100%, respectively. In this ex vivo model, the authors noted that 50% of midazolam was lost within 1 hour of drug addition to the ECMO circuit, indicating that higher initial doses may be necessary to achieve adequate sedation. In an in vivo analysis,[36] more evidence was provided for increasing drug requirements for patients maintained on ECMO therapy. On average, midazolam requirements increased by 18 mg/day after the commencement of ECMO, which represented a 10.2% increase in dose. It should be noted that deep sedation was the goal, with clinicians titrating sedation to a Riker Sedation-Agitation Scale score of 1–2. Therefore, it is difficult to extrapolate these specific findings to patients requiring lower levels of sedation, but they demonstrate the challenges that clinicians face in maintaining sedation during ECMO therapy.

Dexmedetomidine

Dexmedetomidine is a selective α_2-adrenergic agonist and is unique compared with traditional agents as it produces reliable sedation and analgesia without the risk of respiratory depression and has a profound opioid-sparing effect.[55] Patients receiving this drug are easily arousable, requiring less supplemental agents; however, limited information exists regarding the use of dexmedetomidine for sedation in patients receiving ECMO. Because of the lipophilic nature of dexmedetomidine, flow rates and length of the tubing may affect the adsorption within the ECMO circuit. These factors potentially limit the utility of dexmedetomidine for long-term sedation for ECMO support. In an in vitro model, dexmedetomidine was added to an ECMO circuit to mimic normal plasma concentrations of 0.9 μg/ml.[12] Preoxygenator and postoxygenator samples were assessed at various time intervals

in both new and older circuits. There were no significant differences noted in drug loss at 24 hours between the old and new circuits; however, significant drug loss was noted from baseline throughout the 24-hour period. No significant difference between preoxygenator and postoxygenator samples was noted, indicating that drug loss was regardless of the oxygenator. The lack of control samples is a potential limitation to this analysis as it is difficult to determine in an in vitro analysis whether drug loss was the result of normal PK drug elimination or of deposition within the ECMO circuit since the medication was given as an initial bolus and not a continuous infusion. Dexmedetomidine is metabolized hepatically, making it difficult to determine the effect on drug elimination in an in vitro analysis. Based on this limited information, it is difficult to determine the role of dexmedetomidine in patients receiving ECMO. Based on the benefits noted over the use of benzodiazepines for sedation within the intensive care unit, it should be considered. Because of significant loss over a 24-hour period, increasing doses may be necessary in addition to higher starting doses as a result of approximately 40% loss within 60 minutes.[12]

Propofol

Propofol has been recommended as an alternative to benzodiazepenes for sedation within the intensive care unit. Limited data exist on propofol PK alterations, but studies indicate significant sequestration of the medication to the ECMO circuit.[37] In an ex vivo analysis, a rapid and major decrease in propofol concentration over time was seen compared with controls. These findings were seen as early as 30 minutes after introducing propofol to the circuit.[38] Although the lipophilic nature of the medication is highly indicative of potential drug sequestration, the authors also demonstrated that oxygen exposure resulted in 70% propofol loss after 45 minutes in an in vitro analysis.[38] It appears that higher doses may be necessary over time to maintain concentrations needed for therapeutic response. It is unclear whether this medication will be useful for patients requiring deeper levels of sedation, as higher doses of propofol may predispose patients to propofol-related infusion syndrome. Further in vivo analyses are necessary to better understand the PK of drugs as well as ensure the safety of propofol in patients receiving ECMO.

Fentanyl

Although much of the literature indicates increased fentanyl requirements during ECMO, some evidence suggests otherwise.[8, 36, 39–41] Despite these contradictory reports, fentanyl has been shown to irreversibly bind to the ECMO circuit and cardiopulmonary bypass equipment, likely as a result of fentanyl's high lipophilicity.[14, 42, 43] The results of an ex vivo study suggest that fentanyl may be beneficial as a short-term analgesia, as fentanyl concentrations remained unchanged for up to 3 hours but was completely absent at 24 hours after introduction to the circuit.[18] It is difficult to determine whether these mixed findings are the results of patient heterogeneity, duration of ECMO, ongoing fentanyl loss, or saturation within the circuit. Clinicians should pay particular attention to the potential for developing drug tolerance, organ maturation, and improvement in organ function as patient clinical status improves to appropriately manage pain during ECMO support.

Morphine

As demonstrated with fentanyl, variable clearance has been demonstrated with morphine in neonatal patients receiving ECMO. As early as 1994, it has been demonstrated that morphine clearance is significantly decreased in patients requiring ECMO. It was shown[44] that mean serum morphine concentrations were significantly increased during ECMO (87.6 ± 58.4 μg/ml) compared with after ECMO (35.9 ± 17.1 μg/ml). A later study showed that morphine concentrations were well preserved in both the crystalloid- or blood-primed circuit compared with fentanyl (17.5% morphine loss vs 87% fentanyl loss) after 24 hours of circulation in an ex vivo ECMO circuit.[18] These results were further confirmed in an ex vivo study demonstrating that morphine drug recovery from the circuit and control samples at 24 hours relative to baseline was virtually the same (103% and 97%, respectively).[14] These findings are likely the result of morphine being less lipophilic than fentanyl, making it a potentially superior option when managing patients receiving ECMO. Patients given morphine for analgesia received significantly less supplemental analgesia and had lower rates of withdrawal after therapy.[45] In addition, patients given morphine were discharged an average of 9.5 days earlier than were patients who received fentanyl.[45]

Ketamine

The use of ketamine for sedation-analgesia has not been well described, and limited information regarding PK alterations has been reported. Current experience with ketamine use exists as a case series and case report; however, an international survey demonstrated that 28% of responders used ketamine as a co-sedative in ECMO management.[56] A case series evaluated ketamine use in 26 patients to determine the resulting effect on Richmond Agitation-Sedation Scale scores, decreased concurrent sedative or opioid use, or changes in vasopressor requirements.[46] The authors noted decreases in vasopressor (11 of 26 patients) and sedation-analgesia (9 of 26 patients) requirements within 2 hours of ketamine initiation. Another case report demonstrated similar findings with reduction in opioids and/or sedative dosing following initiation of ketamine infusion.[47]

Sedative and Analgesic Use and Requirements

An international survey evaluating sedation practices in patients receiving VV ECMO showed that midazolam (79%), morphine (43%), and fentanyl (45%) were the most commonly used agents.[56] Despite limited published data on dexmedetomidine, 66% of responders stated that they used this agent for sedation. Only 58% responded that there was a necessity for higher sedation requirements for patients receiving ECMO compared with other critically ill patients.

Until recently, nearly all of the information regarding drug PK and ECMO was based on in vitro or ex vivo analyses. Researchers[57] published an analysis comparing the maximum 6-hour sedative requirements and time to reach this maximum among patients with ARDS who had and who did not have ECMO support. Patients receiving ECMO required nearly twice the amount of sedatives (midazolam equivalents, median [interquartile range]: 118 [48–225] vs 60 [37–99] mg, p=0.004) and reached this point nearly 3 days later than patients not receiving ECMO. Interestingly, patients in the ECMO group were more likely to receive benzodiazepine monotherapy (65% vs 30%, p=0.001) without significant differences in average infusion rate but took 3 days longer to achieve the maximum dose threshold. Significantly higher opioid requirements (fentanyl equivalents, median [interquartile range]: 2950 [1950–7840] vs 900 [300–1575] mcg, p=0.001), on average, were observed in the ECMO group, with fentanyl being the most commonly administered opioid. A multivariable linear regression model was constructed to characterize factors influencing sedative requirements. Patient age (p=0.04) and administration of high-dose fentanyl within 24 hours before ECMO (p<0.001) were associated with the maximum 6-hour sedative exposure. The findings from this study indicate that other factors influence the amount of sedation required outside of ECMO. The authors focused on sedation requirements in patients receiving ECMO, but the retrospective nature of the analysis makes detailing specific clinical outcomes challenging. Future studies should build on this analysis to provide more information on how increased sedative requirements affect clinical outcomes.

Dosing Guidance Based on Physiochemical Properties

Despite increasing ECMO use, a clinical gap remains in the published information on the clinical effects of ECMO on drug PK. More often than not, the only information available is from in vitro or ex vivo studies, which provides a dilemma for the clinician in addition to potential limitations. In this circumstance, it is important to use the available information from previous studies in addition to a drug's physiochemical properties to guide in adjusting dosage regimens (Table 2). Commonly reported physiochemical properties, as previously described, demonstrated to most significantly affect PK changes in patients receiving ECMO include Vd, logP, and protein binding.

Limitations

A significant limitation to using previous information is improved technology as well as differences in available ECMO equipment. Since its inception, oxygenators, pumps, tubing, and other components have evolved to improve safety and sustainability of the circuit, which potentially changes how drugs are affected by these components. Most of the studies evaluated used administration of a single dose of a medication into an in vitro or ex vivo closed-loop circuit and do not take into account the effects of human subjects and the effects of metabolism and elimination. Although concomitant

Table 2. Expected Pharmacokinetic Changes and Dose Adjustments Based on Physiochemical Properties

Volume of Distribution and Loading Doses

Vd	Expected Change in Volume of Distribution	Loading Dose Adjustment
≤ 1 L/kg	Moderate to large increase	Dose increase likely required
> 1 L/kg	Minimal increase	Dose adjustment likely not required

Drug Sequestration Based on Octanol/Water Partition Coefficient and Protein Binding

	Protein Binding		
Octanol/Water Partition Coefficient	< 30%	30–70%	> 70%
< 1	Minimal	Minimal to moderate	Moderate
1–2	Minimal to moderate	Moderate	Moderate to high
> 2	Moderate	Moderate to high	High

Maintenance Dose Adjustment Based on Drug Sequestration

Drug Sequestration	Dose Adjustment
Minimal	Dose adjustment likely not required
Moderate	Increased dose, frequency, or infusion rate may be required
High	Increased dose, frequency, or infusion rate likely required

This table may be used as a tool for predicting pharmacokinetic changes in patients receiving extracorporeal membrane oxygenation and their resulting dose adjustments. A specific drug may be evaluated by sequentially determining loading dose adjustments, sequestration, and maintenance dose adjustments.

drugs are frequently administered in clinical practice, analysis of compatible study drugs in the circuit and control jars may impact competitive binding to proteins or circuit components. With regard to in vivo PK data, the majority are derived from small retrospective studies, case reports, or case series. In addition, there is a great degree of variability in terms of subject characteristics, study methodology, equipment used, and patient care. Given the heterogeneity of the available in vivo data, it would be prudent for clinicians to be cautious when interpreting and clinically applying these data. Ultimately, current data provide limited guidance for dosage adjustments, and these data must be used in conjunction with clinical judgment and close patient monitoring.

Future Directions

With an evolving scope of ECMO use in the adult population, more research is being conducted to evaluate optimization of antimicrobial dosing, sedation, and analgesia. Currently, a multicenter study is being conducted to expand the knowledge of ECMO and the varying impact on drug PK to determine whether the data correlate with those observed in neonatal studies.[58] In addition, the authors seek to develop an evidence-based algorithm from the analysis that can be used in the clinical setting. In accordance with this study, the ECMO PK Project will provide a better understanding of the interplay among drugs, the ECMO circuit, and critical illness factors that may influence PK and pharmacodynamics.[59]

Conclusion

Current knowledge of PK changes of individual drugs in adult patients receiving ECMO support is limited, making optimal dosing of drugs difficult in this population. However, with the limited data available and awareness of each drug's physiochemical properties, some guidance for the adjustment of drug dosage regimens is offered. As new PK data emerge, optimization of pharmacotherapy within this critically ill population continues to move forward.

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