Review Article

Optimising drug dosing in patients receiving extracorporeal membrane oxygenation

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Abstract: Optimal pharmacological management during extracorporeal membrane oxygenation (ECMO) involves more than administering drugs to reverse underlying disease. ECMO is a complex therapy that should be administered in a goal-directed manner to achieve therapeutic endpoints that allow reversal of disease and ECMO wean, minimisation of complications (treatment of complications when they do occur), early interruption of sedation and rehabilitation, maximising patient comfort and minimising risks of delirium. ECMO can alter both the pharmacokinetics (PK) and pharmacodynamics (PD) of administered drugs and our understanding of these alterations is still evolving. Based on available data it appears that modern ECMO circuitry probably has a less significant impact on PK when compared with critical illness itself. However, these findings need further confirmation in clinical population PK studies and such studies are underway. The altered PD associated with ECMO is less understood and more research is indicated. Until robust dosing guidelines become available, clinicians will have to rely on the principles of drug dosing in critically ill and known PK alterations induced by ECMO itself. This article summarises the PK alterations and makes preliminary recommendations on possible dosing approaches.

Keywords: Extracorporeal membrane oxygenation (ECMO); pharmacology; pharmacodynamics (PD); antibiotics; sedatives

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Introduction

Temporary mechanical cardiorespiratory support with the use of extracorporeal membrane oxygenation (ECMO) circuitry in adult patients is a relatively new development in medicine (1-3). Technological advancements have allowed use of these therapies with relative ease and the patient outcomes are promising, even when it is applied as a rescue therapy (4). As ECMO finds its place in modern intensive care unit (ICU), clinical application of this technology needs further refinement to optimise its effectiveness. Currently, there is lack of clarity on many aspects of ECMO management and it may take decades of further research to generate evidence that will guide best practice. There is undoubtedly a learning curve for such complex interventions and clinical application of ECMO is rapidly evolving. For example, sedation on ECMO can be a significant challenge (5,6), but a patient being kept bed-

bound whilst receiving ECMO and with heavy sedation is no longer a common practice in advanced ECMO centres and there is increasing emphasis on early interruption of sedation and use of mobilisation techniques (7-9). Optimal ventilation strategies on ECMO are also unclear and this has a significant bearing on sedation practices. Similarly, modern circuitry has allowed safe conduct of ECMO with low intensity anticoagulation (10). Very few centres now administer prophylactic antibiotics to their ECMO patients. Therefore, pharmacotherapy needs to be applied in a goal-directed fashion. Often, ECMO is a bridge to further long-term devices or transplant (11,12), and once again optimal pharmacotherapy helps clinicians to manage the ECMO run in a manner that minimises complications and maximises the likelihood of a patient receiving destination therapy. A thorough understanding of altered pharmacokinetics/pharmacodynamics (PK/PD) during ECMO is essential to apply pharmacotherapy in these complex patients (13), and this paper aims to provide the necessary background for clinicians and researchers in this field.

Pharmacotherapy to reverse disease

Mechanical support does not necessarily replace pharmacological support and optimal pharmacological management is critical to reverse underlying disease and minimise complications. Such drug therapy may include:

(I) Antibiotics or immunomodulator drugs that are administered to reverse underlying disease;
(II) Sedation and analgesia to minimise pain, discomfort and anxiety;
(III) Anticoagulation to minimise thrombotic risks within the patient and in the circuitry;
(IV) Vasoactive drugs to support circulation or promote native cardiac ejection;
(V) Diuretic agents to assist fluid balance;
(VI) Other general supportive measures.

It is important that these drugs are dosed effectively to achieve desired clinical effect which includes minimising the possibility of drug toxicity. While vasoactive drugs, sedatives, diuretics or anticoagulants can be titrated to real-time observable clinical endpoints, antibiotic dosing is often arbitrary or based on data from critically ill patients not on ECMO, or even from non-critically ill patients (14). This is concerning as reversal of the underlying disease that leads to cardiac and/or pulmonary dysfunction is critical to liberation from ECMO and not all patients may be bridged to other definitive options such as a long-term device or transplantation.

Therefore, the increasing use of ECMO in adult ICUs needs to be accompanied by an in-depth understanding on the potential ECMO-related PK changes and how these alterations may affect dosing requirements. The current challenge therefore is to investigate the ECMO-related PK changes in these drugs to in order to design optimised drug dosing regimens. Extreme PK changes in critically ill patients have been well described (14), and the introduction of ECMO appears to have added an additional level of complexity and importantly, another variable inadequately characterised in adult critical care management (15). Preliminary investigations have demonstrated that the introduction of ECMO potentially leads to significant changes in the PK of drugs in three ways: (I) drug sequestration by the circuit; (II) increased volume of distribution (V_d) and; (III) altered drug clearance (CL).

ECMO and drug sequestration

The interaction between the ECMO circuit and the physicochemical properties of drugs may lead to significant changes in the PK of many important drugs, subsequently altering the dosing requirements for patients on ECMO. An advanced understanding on this intricate interaction is critical to drug dosing in patients receiving ECMO, at least until more robust dosing guidelines become available.

Circuit factors

ECMO circuitry, which includes the conduit tubings and oxygenator membrane, introduces additional extracorporeal volume and increases the surface areas that drugs can be trapped in and adsorbed on. This results in an increase in V_d and subsequent decreases in plasma drug concentrations (15,16). However, the adsorption phenomenon may decrease over time due to saturation of binding sites and it is imperative that dosing of drugs also reflects this situation; applying higher dosing continuously during ECMO to overcome this adsorption phenomenon may later lead to drug toxicity. Conversely, the circuit may serve as a reservoir and redistributes the sequestered drug back into the patient even after the drug administration stops, potentially leading to prolonged undesirable pharmacological effects. Sequestration of drugs can be influenced by the following circuit factors: oxygenator materials (17-19); the types of conduit tubings (19,20); circuit age (20-22) and; the composition of the priming solution (23-25).

Physicochemical characteristics of the drug

The physicochemical properties of a compound determine the interaction of an individual drug with the ECMO circuit. The specific physicochemical characteristics that need to be considered include molecular size, pKa and degree of ionisation, lipophilicity and plasma protein binding (15). Numerous *ex vivo* data have suggested that the degree of lipophilicity and protein binding are significant factors affecting the proportion of drug sequestered within the ECMO circuit (23,24,26-28). The lipophilicity of a drug is generally described by the n-octanol/water partition coefficient (log P); a high positive log P indicates a higher degree of lipophilicity and therefore, drugs with such a property tend to be highly sequestered and extracted by the ECMO circuit than drugs with a lower log P (18,28,29). Additionally, the extent of protein binding may determine the degree of drug sequestration for drugs with similar lipophilicity (26,29).

ECMO and increased volume of distribution

The introduction of ECMO may alter the apparent V_d of drugs by the following mechanisms: (I) drug sequestration; (II) haemodilution from priming solution and; (III) ECMO-related physiological changes. PK changes associated with the systemic inflammatory response syndrome (SIRS) are common in critically ill patients receiving ECMO, potentially leading to an increase in V_d of hydrophilic drugs (30). Furthermore, patients receiving ECMO may have significant changes in blood pH leading to further alterations in drug distribution, degree of ionisation and protein binding (31). Numerous data documenting the relationship between ECMO usage and enlarged V_d mostly originated from *ex vivo* and neonatal PK studies (16,32,33). Hence, the extrapolation of this data to critically ill adult patients may potentially be misleading due to significant physiological and body composition differences between these populations and must be undertaken with caution.

ECMO and drug clearance

In general, ECMO patients have been shown to display lower drug CL when compared with patients not receiving ECMO (16). Lower drug CL and the resultant accumulation of drugs and their metabolites are believed to be caused by renal and hepatic hypoperfusion and hypoxia (34). This phenomenon is sometimes offset by the initial increase of clearance due to increased cardiac output secondary to SIRS, aggressive fluid therapy and inotropic support (30).

Dosing regimens based on the CL of non-ECMO population are often used to guide dosing in ECMO patients due to scarcity of more relevant data. As previously discussed, the PK parameters in this subpopulation are likely to be unique. Much of the current ECMO PK data exist in the neonatal literature (35), but extrapolation from this must be done with caution in the context of the immature glomerular and tubular function, as well as the developing hepatic function of newborns (36).

The impact of ECMO on the PK of antimicrobials

Much of the emphasis and incentive to better understand ECMO-related PK changes stems from the desire to provide optimal antibiotic therapy for critically ill ECMO patients. Optimal antibiotic therapy has been shown to correlate with improved patient outcomes (37-39) and this strategy often underpins the primary treatment goal in this patient population. In comparison to sedatives and vasoactive agents, which can be titrated to effect, antibiotic therapy is guided by laboratory surrogates without any real-time feedback. Suboptimal antibiotic dosing may likely lead to treatment failures and importantly, to the development of bacterial resistance (40). Optimal dosing of antibiotics must consider physicochemical characteristics of the individual drug and its interaction with the circuit (26,28,29). In the absence of robust data guiding antibiotic dosage for patients on ECMO, it is prudent that the use of existing published data is supplemented with therapeutic drug monitoring (TDM) where possible. *Table 1* summarizes the potential PK changes and suggested dosing adjustments for several important antimicrobials during ECMO support.

Beta-lactams

Beta-lactam antibiotics are relatively hydrophilic with varying levels of protein binding. This suggests that there may be inter-class variability in their ECMO-related PK changes. For example, ceftriaxone is ≥85% protein-bound and would likely have higher drug sequestration into the ECMO circuitry than other beta-lactams with lower protein-binding properties (26,29). The beta-lactam's optimal bactericidal killing is achieved when the free (unbound) drug concentration remains four-to-five times above the minimum inhibitory concentration (MIC) of a pathogen for extended periods during a dosing interval ($fT_{>MIC}$) (54,55). Existing dosing regimens aim to optimise

Table 1 Summary of pharmacokinetic changes and potential dosing adjustments for antimicrobials during ECMO

Drug (ref.)	N-octanol/water partition coefficient	Protein binding (%)	Anticipated/reported pharmacokinetic changes	Dosing recommendations & comments
Antibiotics				
Aminoglycosides (41-45)	<0.0	<30	Minimal circuit drug sequestration; enlarged Vd; decreased CL	Insufficient data to recommend optimal dosing[a]; TDM-guided dosing
Beta-lactams				
Ampicillin (24)	1.35	15–30	Minimal to moderate circuit drug sequestration; enlarged Vd	Consider alternative agents; less drug loss in blood-primed *vs.* crystalloid-primed circuit
Ceftriaxone (26,29)	–1.7	95	Significant circuit drug sequestration; enlarged Vd	Dosing similar to critically ill patients not on ECMO support; TDM-guided dosing
Meropenem (46,47)	–0.69	2	Minimal circuit drug sequestration; enlarged Vd; circuit drug loss due to stability issues associated with the carbapenems	Dosing similar to critically ill patients not on ECMO support; TDM-guided dosing; consider alternative dosing strategies (CI or EI dosing)
Piperacillin/tazobactam (46)	0.67	30	Minimal circuit drug loss; enlarged Vd	Dosing similar to critically ill patients not on ECMO support; TDM-guided dosing; consider alternative dosing strategies (CI or EI dosing)
Fluoroquinolones (26,29)	<2.3	20–40	Minimal circuit drug sequestration	Dosing to optimise $AUC_{0\text{-}24}$/MIC[b]
Vancomycin (48-51)	–3.1	50–60	Minimal circuit drug sequestration; enlarged Vd	Dosing similar to critically ill patients not on ECMO support; a loading dose 25–30 mg/kg followed by 30–40 mg/kg/day; TDM-guided dosing; consider CI dosing
Antifungals				
Caspofungin (24,52,53)	<0.17	97	Minimal to moderate circuit drug sequestration	Insufficient and conflicting data; dosing adjustments may be required
Voriconazole (24,52)	1	58	Significant drug sequestration	Higher initial loading dose with higher daily doses; TDM-guided dosing to monitor circuit saturation

[a], due to major refinements in ECMO technology, earlier pharmacokinetic data and dosing recommendations may potentially be irrelevant to current practice; [b], these may be achieved with a 400 mg 8-hourly or 600 mg 12-hourly for ciprofloxacin. ECMO, extracorporeal membrane oxygenation; MIC, minimum inhibitory concentration; TDM, therapeutic drug monitoring.

this index but with the ECMO- and critical illness-related PK changes, the ability to ensure optimal $fT_{>MIC}$ becomes a clinical challenge.

Numerous *ex vivo* model of ECMO circuits (26,28,56,57) and clinical PK studies (46,47,58,59) have investigated beta-lactams PK during ECMO support. The earlier studies demonstrated high variability in drug concentrations with a largely unpredictable PK profile when comparing

ECMO versus non-ECMO patients. However, two recent studies have both suggested that the introduction of the ECMO does not significantly alter the PK of beta-lactams (46,47). As the presence of ECMO has not been found to significantly alter the PK of beta-lactam antibiotics, the recommended dosing strategies for critically ill patients without ECMO support can be applied in this patient population (60). It is also suggested to use beta-lactam TDM during ECMO to maximise therapeutic outcomes (60,61).

Vancomycin

This glycopeptide antibiotic exhibits optimal bacteriological and clinical outcomes when the ratio of area under the concentration-time curve during a 24-hour period (AUC_{0-24}) to MIC (AUC_{0-24}/MIC) is maintained ≥400 (62,63). Early adult and neonatal PK studies suggested that there is an ECMO-related increase in V_d and decrease in CL and as a result alterations in effective vancomycin concentrations (64-66). Many newer studies have not corroborated these earlier findings (48-51). A retrospective PK study showed that conventional intermittent vancomycin dosing may likely be a flawed dosing strategy during ECMO, with 95% of the cohort achieving suboptimal antibiotic exposure (50). However, a matched-cohort study conducted by Donadello *et al.* showed similar V_d and CL between ECMO and non-ECMO patients, who all received continuous vancomycin infusion (51). This suggests that the use of continuous vancomycin infusion during ECMO may potentially negate the ECMO-related PK changes. Higher vancomycin doses may be required if intermittent bolus dosing is used in patients receiving ECMO.

Fluoroquinolones

Similar to vancomycin, optimal bactericidal killing of fluoroquinolones is associated with the AUC_{0-24}/MIC ratio (67). There are limited PK data available on this class of antibiotic in ECMO patients, but an *ex vivo* experiment has suggested that the risk of circuit drug loss is relatively low and potentially insignificant for ciprofloxacin (26). Given other members of the group such as moxifloxacin and levofloxacin have a lower log P values with similar protein binding properties as compared to ciprofloxacin (68), it is therefore anticipated that the degree of sequestration in ECMO circuit for these drugs may also be relatively low. It is highly likely that no dosing adjustment is required when these antibiotics are used during ECMO but dosing should seek to maximise AUC_{0-24}/MIC ratio as this ensures optimal therapeutic outcomes in critically ill patients (67). Nevertheless, more robust PK data are urgently needed to corroborate these preliminary data.

Aminoglycosides

Limited data has been published on the PK of aminoglycosides in the critically ill adult population receiving ECMO. Aminoglycoside exhibits concentration-dependent bacterial killing and optimal therapeutic outcomes have been associated with achieving a ratio of peak drug concentration (C_{max}) to MIC (C_{max}/MIC) ratio of 10–12 (69) and an AUC_{0-24}/MIC ratio of 80–160 (70). Neonatal PK studies have mostly reported an increase in the V_d of gentamicin with a decrease in CL (41-45). However, extreme caution must be taken when extrapolating these findings to the critically ill adult patients given marked differences in patient physiology and rapid evolution of ECMO technology, rendering earlier PK knowledge and dosing recommendations irrelevant to current clinical practice. It is also recommended that TDM should continue to be employed when an aminoglycoside is used in patients receiving ECMO.

Antifungals

Antifungals are heterogeneous group of drugs with varying levels of protein binding and lipophilicity. With limited large-scale PK data, their optimal dosing in ECMO remains arbitrary. Voriconazole demonstrated significant sequestration into the ECMO circuit in an *ex vivo* study (24), with 71% of circuit drug loss being reported, which was expected due to the drug's high log P value and moderate protein binding property (68). Another published case study of voriconazole in ECMO patients corroborated the *ex vivo* finding, highlighting the need for an increased voriconazole dosing for this subpopulation (52). However, Spriet *et al.* also demonstrated time-dependent saturation of the circuit leading to supra-therapeutic concentrations with increased dosing.

The echinocandin antifungal, caspofungin, has also been studied in *ex vivo* model of ECMO circuit reporting a 43% loss due to sequestration (24). However, several reports in critically ill adult patients documented conflicting findings (52,53). Further, larger powered studies are required to investigate the PK of antifungals in patients on ECMO support.

Table 2 Summary of pharmacokinetic changes and potential dosing adjustments for sedatives and analgesics during ECMO

Sedatives and analgesics (ref.)	N-octanol/water partition coefficient	Protein binding (%)	Anticipated/reported pharmacokinetic changes	Dosing recommendations & comments
Benzodiazepines				
Midazolam (5,6,28)	3.9	97	Significant circuit drug sequestration	Higher initial loading dose with higher daily doses
Dexmedetomidine (17,20)	2.8	94–97	Significant circuit drug sequestration	Consider higher initial loading dose with higher daily doses[a]
Opioids				
Fentanyl (24,27,28,74-76)	4.1	80–85	Significant circuit drug sequestration	Consider alternative agents; to be considered only as a short-term analgesia
Morphine (24,27,28,32,33)	0.9	30–40	Minimal to moderate circuit drug sequestration	Higher initial loading dose with higher daily doses
Propofol (23,77)	3.8	95–99	Significant circuit drug sequestration	Insufficient data but likely to require higher doses over time

[a], should be considered due to favourable safety profile when compared to other traditional agents. ECMO, extracorporeal membrane oxygenation.

The impact of ECMO on the PK of sedatives and analgesics

Significant amounts of research have been dedicated towards optimising sedation and analgesia for critically ill patients. Evidence-based sedation protocols, primarily aiming for lighter and minimal sedation, have been suggested to improve therapeutic outcomes in critically ill patient population (9). However, strict adherence to these recommendations may be challenging in critically ill patients receiving ECMO and importantly, may not always be practical in such a scenario. Earlier in the course of extracorporeal support, patients on ECMO usually require deep sedation and paralysis to optimise circuit flows and ventilation whilst eliminating pain, anxiety and other forms of distress induced by the ICU environment (71). Further to this, emerging reports have documented greater sedative requirements are needed for critically ill neonates (33,59,72,73) and adults during ECMO support (5,6). PK studies in neonates have consistently reported increased V_d and decreased drug CL during ECMO (16,35), both of which could potentially explain the heightened sedation requirement observed in this patient cohort. *Table 2* summarizes the potential PK changes and suggested dosing adjustments for several important sedatives and analgesics during ECMO support.

Opioids

Fentanyl, due to its higher degree of lipophilicity (68), appears to be more significantly sequestered in the ECMO circuit as opposed to other drugs. In a recent *ex vivo* experiment, Shekar *et al.* demonstrated that the mean drug loss of fentanyl (97%) to ECMO circuits was relatively higher when compared to those of morphine (0%) and midazolam (87%) (28). This, among other studies (24,27,74-76), corroborates the need to escalate fentanyl doses over time in order to achieve optimal sedation in critically ill patients receiving ECMO (5,6). However, higher fentanyl doses for this cohort may not always be feasible and safe; excessive sedative drug use has been associated with increased patient morbidity in the ICU (78-81). Fentanyl therefore appears to be an inferior option in this population and if it is to be used, it may be considered as a short-term alternative to other agents. In an *ex vivo* model of ECMO circuit, Mehta *et al.* observed that fentanyl concentrations remained stable for up to 3 hours but were undetectable at 24 hours during their experiment (24).

In contrast, the impact of ECMO on morphine PK is less pronounced when compared to fentanyl (24,27,28,32,33). Shekar *et al.* demonstrated that the average morphine recovery from their *ex vivo* model of ECMO circuits at 24 hours was >99% and this suggests that the risk of drug sequestration to the circuit is relatively low and potentially

insignificant for morphine (28). This, among other findings (18,24,27,32,33), may likely stem from the result of morphine being less lipophilic (68), and consequently, making it a superior clinical option as opposed to fentanyl in the management of ECMO patients. Additionally, morphine has also been reported to provide optimal analgesia, whilst reducing drug withdrawal and length of hospital stay significantly.

Although most of the available data noted greater opioid requirements on ECMO, a more recent publication indicated otherwise. In a 2-year, prospective, observational study involving 32 critically ill patients on ECMO, DeGrado *et al.* observed that this cohort required relatively lower doses of opioids than previously described with no dose increments needed throughout the study duration (82). It is imperative to highlight that ≥20% of the cohort were receiving ECMO as a bridge to transplantation and this subgroup of patients commonly requires lower sedative and analgesic doses compared with other indications for ECMO (83). Furthermore, sedation practices vary across different institutions and may contribute to these contradictory findings. DeGrado *et al.* also noted that the patients who received venovenous (VV) ECMO in this study also had significantly higher opioid requirements than those receiving venoarterial (VA) ECMO (82). Approximately half of the VV ECMO patients had acute respiratory distress syndrome (ARDS) and therefore were more likely to need higher doses of sedatives and analgesics, before and during ECMO treatment, to facilitate optimal mechanical ventilation. In contrast, VA ECMO patients may have been fully anaesthetised prior to or during cardiac surgery.

Benzodiazepines

Significant midazolam sequestration has been observed in several neonatal and paediatric ECMO studies (59,84). In an *ex vivo* model of ECMO circuit, Shekar *et al.* aimed to describe midazolam disposition in the adult ECMO circuitry (28). In this experiment, the average midazolam recovery from the ECMO circuits was approximately 13% and more importantly, half of the drug was lost in the circuits within 1 hour of the experiment. This essentially means that higher initial midazolam doses may be required to achieve early and optimal sedation in critically ill patients during ECMO support. These findings are further corroborated by two retrospective cohort studies (5,6), which aimed to characterise sedation requirements in patients receiving ECMO for cardiac and/or respiratory failure. In the first study, Shekar *et al.* reported that the median daily dose for midazolam was 175 mg (range, 24–1,500 mg), representing a 10% increase in daily dose after ECMO commencement (6). Furthermore, these patients were receiving up to 1,500 mg of midazolam/day despite concomitant use of propofol, dexmedetomidine, thiopentone and neuroleptic agents, raising genuine concerns of increased morbidity secondary to excessive sedation. In the second study, Nigoghossian *et al.* documented that ECMO patients required twice as high midazolam 6-hour exposure when compared to patients not on ECMO support (ECMO: 118 mg *vs.* non-ECMO: 60 mg ; P=0.04) and optimal sedation was reached approximately three days later in the ECMO group (5).

However, these earlier findings have since been contradicted by a recent publication and therefore warrant further investigation. In a cohort of 32 critically ill patients receiving ECMO, DeGrado *et al.* recently noted that these patients required significantly lower doses of benzodiazepines (24 mg) than previously documented in the literature and additionally, did not demonstrate a need for dose escalation throughout ECMO treatment (82). When patients who received ECMO as a bridge to transplantation were excluded from analysis, benzodiazepine requirements were significantly higher in the VV ECMO group (VV ECMO: 48 mg *vs.* VA ECMO: 34 mg; P=0.006), similar to what has been reported by Shekar *et al.* (6).

Dexmedetomidine

Dexmedetomidine is unique compared with other traditional agents, because it produces sedation and analgesia without compromising respiratory drive (85,86). However, limited data currently exist on its usage in critically ill patients during ECMO support (17,20,87). Due to the lipophilic nature of the drug, dexmedetomidine appears to be significantly lost through circuit adsorption during ECMO (68). Wagner *et al.* used an *in vitro* model to evaluate the impact of ECMO on the disposition of dexmedetomidine over the course of 24 hours (20). Within the first hour of the experiment, ≥40% of the drugs were lost in the circuits and only ≤30% remained at 24 hours. The investigators further suggested that the significant drug loss was likely due to adsorption to polyvinyl chloride (PVC) tubings and this notion has also been supported by a recent publication (17). The precise role of dexmedetomidine remains unclear in patients receiving ECMO but its

favourable safety profile may be advantageous over other traditional agents. On the basis of the available data, using higher initial loading doses with higher daily doses may be considered to compensate for the anticipated PK changes during ECMO treatment.

Propofol

As propofol is a highly lipophilic and highly protein bound drug (68), it is anticipated to be significantly sequestered within the ECMO circuitry (21,77,88-90). In an *in vitro* study, Hynynen *et al.* showed that approximately 35% and 75% of propofol were lost within the ECMO circuits after 5 and 120 minutes of the experiment, respectively (89). In a recent *ex vivo* model of whole-blood primed ECMO circuit, Lemaitre *et al.* reinforced earlier experimental findings which documented significant propofol loss through circuit adsorption (23). In this study, 70% of drug concentration diminished within the first 30 minutes of the experiment and after 5 hours, only 11% of the initial propofol concentration remained. Although these findings are expected based on the physicochemical properties of propofol, Lemaitre *et al.* also suggested that oxidation may also be an important determinant of propofol PK during ECMO; a 70% decrease in propofol concentrations were noted at 45 minutes post-oxygen exposure in the *in vitro* arm of the study. Based on these limited data, it appears that higher doses of propofol may be required over time for optimal sedation but further studies are needed to investigate the safety of such an approach in ECMO patients.

Anecdotally, in the author's experience, a multimodal strategy of early tracheostomy/extubation where feasible, a combination of enteral longer-acting benzodiazepines and antipsychotics, intravenous short acting benzodiazepine and an opioid (morphine preferred) and dexmedetomidine in titrated doses to clinical endpoints often achieves optimal sedation, analgesia and anxiolysis. Intravenous ketamine can be a useful adjunct. Enteral methadone may be added as the risks of opioid withdrawal after weeks of high dose opioid therapy may be substantial and often excessive sedation is administered to overcome this. Dexmedetomidine, being a negative chronotropic agent can also aid optimisation of oxygenation in VV ECMO patients who have refractory hypoxia on ECMO in the setting of a high native cardiac output. Development of evidence-based sedation and analgesia targets and protocols for ECMO patients may help address this complex issue moving forward.

The impact of ECMO on the PK of other drugs

There are limited data available on the PK of other drugs during ECMO and most of them originated from neonatal and paediatric studies. Scarce PK data are available for several cardiovascular drugs (91-95), diuretics (96-98), phenobarbital (99), ranitidine (100), and theophylline (101), and these studies generally reported altered drug PK and dosing requirements during ECMO support.

Anticoagulants

Optimising anticoagulation in patients receiving ECMO is necessary to prevent some of the common ECMO-related complications, such as bleeding and/or thrombosis. The PK of heparin was studied on five infants receiving ECMO and in this study, Green *et al.* found that more than one-half of the administered heparin was cleared by the circuit itself or by blood components in the circuit (102). Data from an *ex vivo* ECMO model further corroborate this observation whereby approximately 30% and 50% of heparin were lost at 24 hours in the crystalloid- and blood-primed ECMO circuits, respectively (24). A more recent study by Park *et al.* however appears to contradict these earlier findings and their *in vitro* ECMO model essentially highlights the importance of material selection on ECMO-related PK changes (17). In this study, the authors found that heparin concentrations remain unchanged in the different types of tubings and oxygenators tested.

Future directions

In order to optimise drug dosing in critically ill patients receiving ECMO, it is essential that the relative impact of drug, device and critical illness factors are considered and systematically investigated, either in isolation or combination. This can be achieved by integrating pre-clinical findings (e.g., *ex vivo* and animal ECMO models) with data from critically ill ECMO patients and through these processes, the PK of a drug and sources for its variability can be described and importantly, optimal dosing recommendations could be suggested for this patient population. In this respect, the ECMO PK Project (103) and the ASAP ECMO Study (104) are two prime examples of such an approach, combining mechanistic and clinical research to investigate PK alterations during ECMO. Data from the two studies will identify the drugs that are most suitable to be used during ECMO and strategies to

optimise dosing in critically ill patients receiving ECMO in accordance to PK/PD principles. Until robust dosing guidelines become available, physicochemical properties of drugs can be used to predict PK changes and consequently, guide effective dosing in this patient population.

Conclusions

Optimised pharmacotherapy enhances the effectiveness of ECMO and is crucial to its success. Clinicians should use available therapeutic drugs in a manner that allows the best possible clinical application of ECMO. Further refinements in clinical application of ECMO will provide clear PD endpoints for many of the drugs that are commonly used on ECMO. In the meantime, pending population PK data and dosing guidelines, a sound understanding of altered PK in critically ill and those on ECMO will serve a guide to drug dosing on ECMO.

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Footnote

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