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Population Pharmacokinetics in Critically Ill Neonates Undergoing Extracorporeal Membrane Oxygenation: A Literature Review

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Abstract

Background: Neonatal extracorporeal membrane oxygenation (ECMO) increases circulating blood volume, capillary leak, and temporarily alters kidney function. Consequently, pharmacokinetics (PK) can be affected. When applied to neonates, additional dose adjustments are a major concern, as the volume of distribution (Vd) is already generally greater for water-soluble drugs and the clearance (Cl) of drugs eliminated by glomerular filtration is reduced in neonates. The aim of this paper is to determine the qualitative effect that ECMO circulation for neonates on PK and to what extent dosing regimens need adjustments.

Methods: A systematic search was performed on MEDLINE® (1990-2022) using a combination of the following search terms: population PK, neonate/newborn, and ECMO. Titles and abstracts were screened, and inclusion/exclusion criteria were applied. Finally, relevant full texts were read and evaluated in terms of PK and dose adjustments.

Results: A total of 121 articles were retrieved, and 15 articles were included after the application of inclusion/exclusion criteria. Since one article was a follow-up to another article with the same study protocol and population, the remaining 14 articles were reviewed in terms of changes in Cl, Vd, elimination half-life ($t_{1/2}$), and recommended dose adjustments. Five out of 14 studies on 6 different drugs (vancomycin, gentamicin, midazolam, phenobarbital morphine, and ranitidine) recommended dose increase/decrease by determining PK parameters. In other studies, it has been suggested to adjust the dose intervals. While the $t_{1/2}$ and Vd mostly increased for all drugs, the Cl of the drugs has been shown to be reduced except for midazolam and morphine.

Conclusion: There are a limited number of population PK studies. Despite some divergences, the general pattern suggests an increase in Vd and $t_{1/2}$, a stable to decreased Cl, and an increase in variability. Consequently, and if possible, therapeutic drug monitoring and target concentration intervention are strongly recommended to determine appropriate exposure and doses for neonates undergoing ECMO.

Keywords: neonates; pharmacokinetics; ECMO; antibiotics; anticonvulsants; sedo-analgesics

What is already known on this topic

- Extracorporeal membrane oxygenation (ECMO) is a proven effective intervention in neonates with severe respiratory or circulatory failure. The increase in the effective circulating volume, changes in blood flow, capillary leak and drug adsorption to components of the ECMO circuit affect pharmacokinetics (PK), also in neonates.

What this study adds

- This current systematic search provides population PK data on 6 different drugs (vancomycin, gentamicin, phenobarbital, midazolam, morphine, and ranitidine), reflecting the relevant knowledge progress made.
- A significant increase in elimination half-life ($t_{1/2}$) is observed in neonates undergoing ECMO, be it that the extent differs between drugs and reports (vancomycin +27.0% to 194.7%, gentamicin +3.9% to 75.4%, midazolam +389.7%, ranitidine +91.6%), and the variability in PK estimates during ECMO increases.

How this study might affect research, practice or policy

- Because of these PK changes, therapeutic drug monitoring and target concentration intervention are strongly recommended to determine appropriate exposure and doses for neonates undergoing ECMO.

INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) is a cardio-pulmonary bypass technique designed to temporarily support respiratory or cardiac function in critically ill patients, including neonates.[1 2] ECMO has two cannulation techniques: veno-venous (VV) and veno-arterial (VA). Veno-venous ECMO is mainly used for patients with respiratory failure, while veno-arterial ECMO support is used in patients with cardiac or respiratory failure.[3 4]

While polypharmacy is known to be common among hospitalized adults, it was reported that it is also highly prevalent among hospitalized children and neonates in the intensive care units (ICU). Because survival and overall outcome rely on medicines, effective drug therapy is essential to improve care and minimize adverse effects.[5 6] This includes, but is not limited to targeted dosing and exposure, but necessitates information on PK changes related to ECMO use in this specific population of neonates.

The main drivers of pharmacokinetics (PK) of drugs are volume of distribution (Vd), which describes the dose required to produce the desired peak concentration, and clearance (Cl), which is the volume of fluid cleared of drug from the body per unit of time. Both Vd and Cl are primary determinants of elimination half-life ($t_{1/2}$). The $t_{1/2}$ can be calculated with the following formula:

- $t_{1/2}$ = 0,693 * Vd/Cl

Although an approximate, from a clinical point of view, this formula relates $t_{½}$ to Vd, CL, and steady-state, which represent the basic PK parameters.[7]

Safe and effective prescription in neonatal ECMO depends on understanding the determinants affecting drug PK and PD in the complex context of patient immaturity, critical illness, (multi)organ failure, and the need for supportive extracorporeal circuits.[8] Because ECMO increases the circulating blood volume, capillary leak, and transiently alters renal function, the PK of many drugs can be affected. In addition, the PK of many drugs in neonates is different from those in adults. All these PK processes (absorption, distribution, metabolism and elimination, ADME) display maturation (age or weight-dependent changes) but are also affected by non-maturational covariates (disease, environment, treatment, co-medications,

genetic background).[9] The Vd in neonates is usually larger for water-soluble drugs. Therefore, the volume of distribution is generally increased, whereas Cl is decreased in neonates undergoing ECMO.[10] Furthermore, differences in the Vd of the drug related to body composition, blood flow, protein binding, and membrane permeability in neonates.[11] The aim of this literature review is to provide an overview on the effects of ECMO on drug PK in neonatal ICU patients, and whether dosing regimens need to be adjusted, or practices adapted.

METHODS

A systematic literature search was performed on MEDLINE® of all literature between January 1990 and January 2022. The search was made using of following keywords 'population PK', 'neonate/newborn', and 'ECMO'. In MEDLINE® the corresponding MeSH terms for these search terms were used. Papers meeting the following criteria were accepted for the study;

- Full-text written in English,
- Concerned the human species,
- Research articles,
- The reporting of a PK parameter for at least one of the absorption, distribution, metabolism, or excretion (ADME) process,
- Full-text is available.

Articles were excluded if the study population did not include neonates, or if ECMO was not applied. Also, case reports and case series were excluded, as we only focused on population pharmacokinetic studies.

First, the titles of all articles were screened. If the relevance was unsure, the abstract was subsequently read. Finally, the resulting selected articles were thoroughly studied, and the references were screened for secondary inclusion after both authors (NS and NY) reach a consensus.

Patient and public involvement

This research was conducted without patient or parent involvement. Patients or parents were not invited to comment on the study design and were not consulted to develop patient-relevant outcomes or interpret the results. Patients or parents were not invited to contribute to the writing or editing of this document for readability or accuracy.

RESULTS

In this search, 121 articles were retrieved with the keywords 'population PK', 'neonate', and 'ECMO' in the MEDLINE® database. After applying the inclusion and exclusion criteria, 15 articles were assessed to be eligible for inclusion. 106 articles were excluded because they did not meet the inclusion criteria (**Figure 1**). Of the 15 articles retained, one article was a follow-up to another article with the same study protocol and population. This article is not included in the tables but is discussed under the relevant heading. A flow diagram of data selection, reasons for exclusion, and subsequent results are provided in **Figure 1**.

Characteristics of included studies (n=14) are provided in **Table 1**. One of the included studies was both prospective and retrospective. Most of the drugs studied are antibiotics (vancomycin and gentamicin), followed by antiepileptics. The route of administration was intravenous in all the studies. Therefore, enteral absorption was not evaluated. Studies were limited to the mother compounds, except for data on the PK parameters of the midazolam and morphine metabolites. Vd and Cl parameters were reported in all studies.

Most studies evaluated both VV and VA modalities of ECMO together. Only one study did not specify the modality. In one study, PK differences between VA and VV were the topic of interest.[12] In this study, there was no statistically significant between VA and VV bypass type in terms of Vd (0.61 ± 0.15 vs. 0.74 ± 0.23 L/kg), Cl (0.157 ± 0.046 vs. 0.199 ± 0.085 L/h), and $t_{1/2}$ (10.04 ± 2.45 vs. 10.75 ± 3.43 h) (p>0.05).[12]

To facilitate comparison of PK parameters described in the articles retained, the quantification of these parameters can be found in **Table 2**. Because of the different characteristics of each drug administered during the ECMO circulation, the included studies as presented in **Table 2** were sorted by drug to facilitate comparison.

Drugs

Vancomycin: Almost consistent results were observed for vancomycin Cl, while findings on Vd were consistent between the 4 studies retrieved. In the study of Cies et al.[13], the vancomycin Cl increased in the presence of ECMO, so that it was suggested to use a higher dose in these patients. The authors attributed this increased Cl to the specific ECMO circuit used. In the other 3 articles, it was shown that the Cl of vancomycin decreased and the $t_{1/2}$ increased.[14-16] In addition, in these 4 articles, the Vd of vancomycin increased in the presence of ECMO, be it not statistically significant in the individual studies.

Gentamicin: Four articles examining the PK of gentamicin in the presence of ECMO were reviewed. In the first reported study of Southgate et al.[17], it was shown that the Vd of gentamicin increased and Cl decreased so that the $t_{1/2}$ further increased in the presence of ECMO. In the studies of Cohen et al.[18], there are similar results in terms of pharmacokinetic parameters of gentamicin. They also recommended that the dose of gentamicin be reduced by 25% and at longer dosing intervals in patients undergoing ECMO therapy, reflecting the extended time interval strategy currently applied for aminoglycosides.[18] Bhatt-Mehta et al.[12], examined the PK parameters in two different modalities of ECMO (VV versus VA) in their study and reported that they could not find a statistically significant difference between both modalities. Finally, a comparison of Munzenberger et al.[19] between ECMO and non-ECMO cases failed to demonstrate any significant impact of ECMO on the PK of gentamicin from the 1st and 2nd set of samples following the initiation (mean days of both sample collection was 2 and 4, respectively).

Phenobarbital: In the first of the two studies, it was reported that the PK parameters of phenobarbital did not differ in neonates and infants undergoing ECMO. Body weight was the main PK covariate of phenobarbital disposition in this study.[20] In the second study by Michaličková et al., it was shown that the Vd of phenobarbital was not much affected by ECMO, while its Cl increased over time, especially in the first 12 days.[21] Both (body weight and postnatal age) rather reflect maturational covariates. Furthermore, there was still high unexplained variability.[21]

Midazolam: Two articles reported on midazolam PK in patients undergoing ECMO. Mulla et al.[22] reported that both the Vd and $t_{1/2}$ of midazolam increased. Clearance was 1.4 (SD 0.15)

ml/kg/min, so that simulations with conventional doses resulted in excess levels. Besides, Ahsman et al.[23] reported an increased Vd and $t_{1/2}$, as well as a 3-fold increase in midazolam and 1-hydroxy-midazolam Cl in the first 5 days following ECMO initiation. Interestingly, concomitant inotropic infusion during ECMO increased 1-hydroxy-midazolam glucuronide Cl by 23%. They also determined the 1-hydroxy-midazolam/midazolam metabolic ratio (MR), a surrogate measure of cytochrome P450(CYP)3A activity, as being higher than previous reports in (pre)term neonates and attribute the reduced renal elimination Cl of the metabolite.

Morphine: Two articles evaluating the PK of morphine in neonates undergoing ECMO were retained. The study population of both studies appears to be the same. While the PK of morphine was evaluated in the first study by Peters et al.[24], the morphine metabolite was added in the second study.[25] In the first study, Cl in neonates [postnatal age (PNA) <7 days] at the start of ECMO (2.2 l per hour per 70 kg) was lower than that in postoperative neonates (10.5 l per hour per 70 kg) but increased rapidly (maturation $t_{1/2}$ 30 and 70 days, respectively) to equal that of the postoperative group from 14 days onwards. The authors stated that Cl was affected by size and age only and that Vd increased with age and was 2.5 times higher in neonates undergoing ECMO than in postoperative cases. Similar to the findings on phenobarbital, the coefficient of variation was significantly higher in neonates on ECMO when compared to postoperative cases.[21,25]

Morphine-3-glucuronide (M3G) was the predominant metabolite. In the study evaluating the PK of M3G, elimination Cl of M3G was lower in the neonates on ECMO, attributed to reduced renal elimination clearance. These elimination clearances were positively correlated with ECMO flow and negatively correlated with dopamine dose.[25]

Ranitidine: In the study by Wells et al., plasma concentrations of ranitidine at 24, 48, and 72 h were determined in neonates who undergoing ECMO. Accordingly, it was reported that the renal and hepatic Cl of ranitidine did not change in these patients within the time window (72 h) studied.[26]

DISCUSSION

Most of the studies included in the review were on vancomycin and gentamicin. Both drugs are drugs with a rather low Vd (L/kg), hydrophilic, and a narrow therapeutic range. Vd relates the amount of drug in the body to the plasma concentration of the drugs, depending on the fluid in which concentration is measured.[27] Vd depends on substance characteristics and patient factors which can be different between neonates and adults. In general, alterations in tissue distribution resulting from a critical illness are more likely to be clinically significant for hydrophilic drugs which do not display useful intracellular penetration and thus have a relatively low Vd.[28] Also, neonates have a proportional higher body water content which can imply that the Vd per kg is higher for water-soluble compounds.[29] In addition to all these factors, it is reasonable to expect that the Vd of hydrophilic drugs will increase with the addition of ECMO circulation. This can be attributed to the circuit itself, as well as to the additional capillary leak commonly observed in these patients. To further illustrate this, all studies examining vancomycin and gentamicin consistently showed an increased Vd in neonates undergoing ECMO.

The Cl of vancomycin is reduced in neonates undergoing ECMO, with the exception of one study[13], and an increased $t_{1/2}$. Accordingly, it is recommended to extend the interval and/or adjust the dose by therapeutic drug monitoring, especially in newborns in the early period (PNA <7 days). Similar to vancomycin, Cl of gentamicin is also decrease. Prolonging the interval of gentamicin, which has a predominant post-antibiotic effect, appears to be more reliable in neonates, as an extended time interval is currently applied for aminoglycosides.

Phenobarbital is an anticonvulsant still commonly used in neonates and infants undergoing ECMO to treat seizures (18-20%) and withdrawal symptoms, with midazolam as a commonly used second-line drug to treat seizures or to sedate the newborn.[20] While it was stated that the distribution of phenobarbital, a lipophilic drug, was not affected by ECMO, it was shown in two studies that the distribution of midazolam increased. Pokorná et al.[20] found similar high inter-individual PK variability for Vd and Cl and no statistical differences in Vd or Cl. The authors assumed that the physicochemical characteristics of phenobarbital resulted in differences in the distribution in comparison with ECMO-induced changes for typical lipophilic drugs. Michaličková et al.[21] found that the phenobarbital Cl increased in the time interval (day

1-12) studied within 12 days. Different loading and maintenance doses were used in both studies, and different Vd and Cl values were calculated. Due to high unexplained variability, frequent and repeated therapeutic drug monitoring should be considered in individual cases, even with the model-derived regimen.[21]

Mulla et al.[22] have analyzed the PK of midazolam in neonates undergoing ECMO. Their midazolam model reveals a significantly altered Vd in ECMO patients, with a significant prolongation of the $t_{1/2}$ (from 6.8 to 33.3 hours). Mulla et al.[22] did not report a correlation between Cl and duration of infusion or PNA. They also determined the MR, a surrogate measure of CYP3A activity, as being higher than previous reports in (pre)term neonates and attribute this to a reduced renal elimination Cl of the metabolite. Similarly, in the study of Ahsman et al.[23], it was shown that the Vd increased. But unlike Mulla et al.[22], they stated that Clincreased 3-fold within the first 5 days. It is estimated that this is due to the difference in the ECMO circuit construction (oxygenator). Ahsman et al.[23] also reported that concomitant inotropic infusion increased hydroxy-midazolam glucuronide Cl by 23% and midazolam dose could be increased starting from the 5th day.

Peters et al.[24] found that morphine Cl on starting ECMO lagged behind that in healthier postoperative neonates of the same age but matured rapidly and was similar to the cohort of postoperative surgical neonates within two weeks. After this study, on the contrary, the same authors found that formation Cl to M3G is reduced during the first ten days of ECMO with the same study population.[25]

CONCLUSION

The aim of this paper was to determine the effect of ECMO use on PK in neonates, based on a systematic assessment of population PK studies. At present, there are a limited number of population PK studies for a limited number of compounds reported in neonates undergoing ECMO. Despite some differences in results for the same drug, the general pattern suggests an increase in Vd and $t_{1/2}$, a stable to decreased Cl, and an increase in variability on ECMO. Consequently, and if possible, therapeutic drug monitoring and target concentration intervention are strongly recommended to determine the appropriate exposure and doses for neonates undergoing ECMO.

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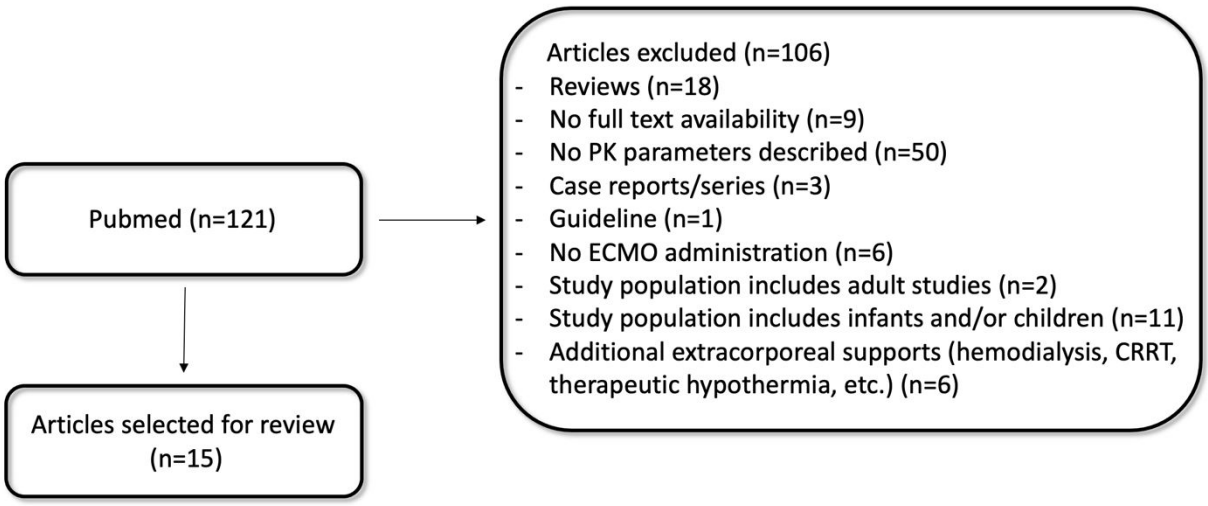
Figure 1. Flow diagram of data selection and subsequent results



PK: pharmacokinetics, ECMO: extracorporeal membrane oxygenation, CRRT: continuous renal replacement therapy

Table 1. Study characteristics (N=14)

Characteristics	**n (%)**
Type of Study	
Prospective observational	7 (50%)
Retrospective observational	6 (42.9%)
Mixed	1 (7.1%)
Drug	
Vancomycin	4 (28.6%)
Gentamicin	4 (28.6%)
Midazolam	2 (14.3%)
Phenobarbital	2 (14.3%)
Morphine	1 (7.1%)
Ranitidine	1 (7.1%)
ECMO Modality	
Veno-venous	2 (14.2%)
Veno-arterial	4 (28.6%)
Mixed	8 (57.2%)
Pharmacokinetic Parameters	
Absorption	-
Distribution	14 (100%)
Metabolic clearance	2 (14.2%)
Excretion	14 (100%)
Elimination half-life	12 (85.8%)

Table 2. Characteristics of the studies, pharmacokinetics, and dose recommendations (N=14)

Study	Drug	n	Type	Modality	Administered Dose	V_d	C_L	$t_{1/2}$ (hours)	Recommended Dose
Buck et al.[14]	Vancomycin	15	R	VV-VA	10mg/kg q8h	0.45 ± 0.18 L/kg **↓15.4%**	0.65 ± 0.28 mL/min/kg **↓21.5%**	8.29 ± 2.2 **↑27.0%**	10 mg/kg q8h
Mulla et al.[15]		15	P&R	VV-VA	10–15mg/kg q6-24h	0.45 ± 0.1 L/kg	0.04± 0.02 L/kg/h	10.40 ±6.67	-
Cies et al.[13]		12	R	VV-VA	10–15mg/kg q8-24h	1.2 ± 0.4 L/kg	3.48 ± 1.31 mL/min/kg	14.1 ± 6.9	10–15mg/kg q8-24h or CI
An et al.[16]		25	R	VV	10mg/kg q8-12h	0.63±0.30 L/kg **↑10.5%**	0.03±0.02 L/kg/h **↓62.5%**	17.45±11.01 **↑194.7%**	0-7 days: 10mg /kg q12h 7-44 days: 10mg /kg q8h
Southgate et al.[17]	Gentamicin	10	P	VV-VA	2.5 mg/kg q12 h	0.51± 0.11 L/kg	2.78 ± 1.55 mL/min	573± 263 min	2.5 mg/kg q18 h
Cohen et al.[18]		12	P	VA	2.5-3 mg/kg q18-24h	0.58± 0.04 L/kg **↑28.9%**	42 ±3 mL/kg/h **↓35.7%**	10.0± 0.7 **↑75.4%**	Reduce dose by 25%
Munzenberger et al.[19]		15	P	-	2.5 mg/kg q12 h	0.62 L/kg **↓1.6%**	0.99 mL/min/kg **↓15.4%**	7.9 **↑3.9%**	-
Bhatt-Mehta et al.[12]		29	R	VV-VA	2.5 mg/kg q12 h	VA: 0.61± 0.15 L/kg VV: 0.74 ± 0.23 L/kg	VA: 0.157±0.046 L/h VV: 0.199±O.086 L/h	VA:10.0±42.45 VV:10.75±3.43	2.5 mg/kg q18 h
Pokorná et al.[20]	Phenobarbital	7	R	VV-VA	LD: 40 mg/kg MD: 40 mg/kg q8-12h	0.46±0.24 L/kg **↓6.1%**	8.0±4.5 mL/h/kg **↓6.1%**	46.1±27.7	LD: 15 mg/kg MD: 4 mg/kg/d
Michaličková et al.[21]		13	R	VV-VA	LD: 7.5mg/kg (8.5–16mg/kg) MD: 6.9mg/kg/d (4.5–8.5 mg/kg/d).	2.72 L	0.0096 L/h	-	In the first 12 days of ECMO with a regimen of a LD of 20 mg/kg and a MD of 4 mg/kg/d divided in two doses with an increase of 0.25 mg/kg every 12 hours during ECMO
Mulla et al.[22]	Midazolam	19	P	VV-VA	50-250 μg /kg/h	4.1±0.5 L/kg **↑412.5%**	1.4 ± 015 mL/kg -	33.3 (7.4-178) **↑389.7%**	LD: 350 μg /kg/h for 6 hours MD: 50 μg /kg/h
Ahsman et al.[23]		20	P	VA	LD: 0.2 mg/kg bolus MD: 0.1 mg/kg/h CI	Midazolam: 14.6 L/3kg 1-hydroxymidazolam: 10.2 L/3 kg	Midazolam: 1.38 L/h/3 kg 1-hydroxymidazolam: 1.03 L/h/3 kg	1.85 -	LD: 300 μg /kg/h for 6 hours MD: 150 μg /kg/h

						Hydroxymidazolam glucuronide: 1.21 L/3 kg **↑240.3%**		Hydroxymidazolam glucuronide: 0.18 L/h/3 kg **↑300.0%**		
Peters et al.[24]	Morphine	14	P	VA	LD: 100 μg /kg MD: 40 μg /kg/h	Day 1: 1.89 mL/kg/min Day 10: 3.33 mL/kg/min **↑76.2%**		Day 1: 1.1 mL/kg/min Day 10: 6.0 mL/kg/min **↑445.5%**	-	-
Wells et al.[26]	Ranitidine	13	P	VA	LD: 2mg/kg 10 min MD: 2mg/kg q24h for 72h	Single dose	1.80±0.55 L/kg **↑15.5%**	0.252±0.154 L/kg/h -	5.64±2.49 **↑91.6%**	LD: 2mg/kg 10 min MD: 2mg/kg q24h for 72h
						72nd hour	-	0.34±0.37 L/h/kg	5.74±2.55	

VV: Veno-venous, VA: veno-arterial, R: Retrospective, P: Prospective, LD: Loading dose, MD: Maintenance dose, CI: Continuous infusion

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Population Pharmacokinetics in Critically Ill Neonates and Infants Undergoing Extracorporeal Membrane Oxygenation: A Literature Review

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Abstract

Background: Extracorporeal membrane oxygenation (ECMO) increases circulating blood volume, capillary leak, and temporarily alters kidney function. Consequently, pharmacokinetics (PK) can be affected. When applied to neonates and infants, additional dose adjustments are a major concern, as the volume of distribution (Vd) is already generally greater for water-soluble drugs and the clearance (Cl) of drugs eliminated by glomerular filtration is reduced. The aim of this paper is to determine the qualitative effect that ECMO circulation on PK and to what extent dosing regimens need adjustments in neonates and infants.

Methods: A systematic search was performed on MEDLINE® (1994-2022) using a combination of the following search terms: "pharmacokinetics", "extracorporeal membrane oxygenation", and "infant, newborn" using MeSH search strategy. Titles and abstracts were screened, and inclusion/exclusion criteria were applied. Finally, relevant full texts were read and evaluated in terms of only population pharmacokinetics and dose adjustments.

Results: A total of 80 articles were retrieved, and 19 articles were included after the application of inclusion/exclusion criteria. Since one article was a follow-up to another article with the same study protocol and population, the remaining 18 articles were reviewed in terms of changes in Cl, Vd, elimination half-life ($t_{1/2}$), and recommended dose adjustments. Nine out of 18 studies on 11 different drugs (vancomycin, meropenem, fluconazole, gentamicin, midazolam, phenobarbital, theophylline, clonidine, morphine, cefotaxime, and cefepime) recommended dose increase/decrease by determining PK parameters. In other studies, it has been suggested to adjust the dose intervals. While the $t_{1/2}$ and Vd mostly increased for all drugs, the Cl of the drugs has been shown to be variability except for midazolam and morphine.

Conclusion: There are a limited number of population PK studies in neonates and infants undergoing ECMO circuits. Despite some divergences, the general pattern suggests an increase in Vd and $t_{1/2}$, an increased, stable or decreased Cl, and an increase in variability. Consequently, and if possible, therapeutic drug monitoring and target concentration intervention are strongly recommended to determine appropriate exposure and doses for neonates and infants undergoing ECMO support.

Keywords: neonates; infants; pharmacokinetics; ECMO; antimicrobials; anticonvulsants; sedo-analgesics

What is already known on this topic

- Extracorporeal membrane oxygenation (ECMO) is a proven effective intervention in neonates and infants with severe respiratory or circulatory failure.
- The increase in the effective circulating volume, changes in blood flow, capillary leak and drug adsorption to components of the ECMO circuit affect pharmacokinetics (PK).

What this study adds

- This current literature search provides population PK data on 11 different drugs (vancomycin, meropenem, fluconazol, gentamicin, midazolam, phenobarbital, theophylline, clonidine, morphine, cefotaxime, and cefepime), reflecting the relevant knowledge progress made.
- An increase in volume of distrubition (Vd), with still high inter- and intraindividual variability in PK parameters of many drugs in ECMO cohorts is observed.

How this study might affect research, practice or policy

- Because of these PK changes, therapeutic drug monitoring and target concentration intervention are strongly recommended to determine appropriate exposure and doses for neonates and infants undergoing ECMO.

INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) is a cardiopulmonary bypass procedure used to provide temporary respiratory or cardiac support to critically ill patients, including neonates and infants.[1 2] ECMO has two cannulation techniques: veno-venous (VV) and veno-arterial (VA). Veno-venous ECMO is mainly used for patients with respiratory failure, while veno-arterial ECMO support is rather used in patients with cardiac failure.[3 4]

While polypharmacy is well recognized in hospitalized adults, it is also quite common in hospitalized neonates and infants in intensive care units (ICU). Because survival and overall outcome rely on medicines, effective drug therapy is essential to improve care and minimize adverse effects.[5 6] This includes targeted dosing and exposure, but necessitates understanding and data on pharmacokinetic (PK) changes related to ECMO use in this specific population of neonates.

Volume of distribution (Vd), which specifies the dosage necessary to generate the desired peak concentration, and clearance (Cl), which is the volume of fluid cleared of drug from the body per unit of time, are the fundamental drivers of drug pharmacokinetics (PK). Vd and Cl are also important drivers of elimination half-life ($t_{1/2}$). The $t_{1/2}$ can be calculated with the following simple formula:

- $t_{1/2} = 0.693 * Vd/Cl$

Although an approximate, from a clinical point of view, this formula relates $t_{½}$ to Vd, CL, and steady-state, which represent the basic PK parameters.[7]

Understanding the parameters impacting medication PK and PD in the complicated setting of patient immaturity, severe illness, (multi)organ failure, and the necessity for supportive extracorporeal circuits is crucial for safe and successful prescription in neonates and infants undergoing ECMO.[8] Many medications' PK can be impacted by ECMO since it raises circulating blood volume, causes capillary leak, and temporarily affects renal function.

The underlying mechanisms related to the additional (non)-maturational changes in PK during ECMO are diverse, and in part related to the ECMO equipment, the impact of the technique, and the medical condition of the neonates and infants.[9] The ECMO equipment alters drug

exposure through adsorption by circuit components. This is to a certain extent drug-specific, and is more pronounced for drugs with high lipophylicity.[10] The need for ECMO will results in shift in fluid balance, capillary leak, and also in renal impairment; Acute kidney injury (AKI) is common in ECMO or cardiac bypass cases.[8 11 12] Finally, the medical condition like sepsis, or cardiac failure in itself will affect PK.[13] These non-maturational factors add on to the maturational PK of many drugs in neonates, different from those in adults.

All of these PK parameters (absorption, distribution, metabolism, and elimination, or ADME) exhibit maturation (age or weight-dependent alterations), but they are also influenced by non-maturational variables (disease, treatment, co-medications, environment or genetic background).[13] The Vd in neonates is usually larger for water-soluble drugs. Therefore, the Vd is generally increased, whereas Cl is decreased in neonates undergoing ECMO, especially for drugs cleared by renal route.[10-12] There are some variations in the Vd due to body composition, blood flow, protein binding, and membrane permeability.[14] Because renal clearance of metabolites is decreased in preterm and term infants, active metabolites may accumulate.[15]

According to the current literature, we aware that many pharmacological treatments in neonates and infants undergoing ECMO have not been fully studied and the risk-benefit ratios are not clearly defined. The aim of this literature review is therefore to provide an overview of the effects of ECMO on drug PK parameters in neonates (postnatal age 0-28 days) and infants (birth to 1-year old), specifically clearance, Vd, $t_{1/2}$ with recommended doses.

METHODS

A systematic literature search was performed on MEDLINE® (National Library of Medicine PubMed) of all literature between January 1994 and February 2022 in the PubMed database in September 2022. The search was made using of following keywords "pharmacokinetics", "extracorporeal membrane oxygenation", "infant, newborn". In MEDLINE® the corresponding MeSH search strategy for these search terms as the main heading (descriptor) were used.[16] 'AND' was used to separate the main search terms. Papers meeting the following criteria were accepted for the study:

- Full-text written in English,
- Concerned the human species,

- Research articles (clinical study, comparative study, multicenter study, observational study etc.),
- The reporting of a PK parameter for at least one of the absorption, distribution, metabolism, or excretion (ADME) process,
- Full-text is available,
- The references and citations of the retained papers were checked (backward snowball method),
- If necessary, additional paper added by the authors.

Articles were excluded if the study population did not include neonates/infants, or if only ECMO (like e.g., concomitant continuous renal replacement therapy (CRTT)) was not applied. Also, case reports, case series, reviews, commentaries, and guidelines were excluded, as we only focused on population pharmacokinetic studies. Physiologically based pharmacokinetics and TDM studies were excluded. Full-texts for all papers were retrieved through various research databases.

First, the titles of all articles were screened. If the relevance was unsure, the abstract was subsequently read. Finally, the resulting selected articles were thoroughly studied, and the references were screened for secondary inclusion after both authors (NS and NY) reach a consensus. All references and citations to the included articles verificated, and no additional studies were identified to be included. Furthermore, an additional search was performed by the authors using the keywords "pharmacokinetics", "extracorporeal membrane oxygenation" and "paediatrics" from MeSH search terms to identify studies with the paediatric population that included newborn and/or infant patients undergoing ECMO circuit.

Patient and public involvement

This study was done without the participation of patients or parents. Patients or parents were not invited to comment on the trial design, nor were they contacted to define patient-relevant outcomes or interpret the findings. Patients or parents were not asked to help write or revise this text for readability or accuracy.

RESULTS

In this search, in total 16 papers were retained with the keyword's "pharmacokinetics", "extracorporeal membrane oxygenation", "infant, newborn". One article related morphine metabolite was excluded because it was a follow-up to another article with the same study protocol and population.[17] There are also 3 additional papers from 135 results added by the authors from children's studies including newborns and/or infants' data. In this manner, the literature review was completed with a total of 18 papers. The articles were published in the MEDLINE® database starting in 1994 (1 report before 2000, 4 between 2000-2009, 7 between 2010-2019, and already 6 reports from 2020 onwards), with a variety of nations participating (depending on the corresponding author). There were no additional articles were found matching the inclusion criteria with the backward snowball method. A flow diagram of data selection, reasons for exclusion, and subsequent results are provided in Figure 1.

Characteristics of included studies (n=18) are provided in Table 1. One of the included studies was both prospective and retrospective. Most of the drugs studied are antibiotics (vancomycin, meropenem, fluconazole, and gentamicin), followed by midazolam and phenobarbital. The route of administration was intravenous in all studies. Therefore, enteral absorption was not evaluated. Studies were limited to the mother compounds, except for data on the PK parameters of midazolam and morphine metabolites. Vd and Cl parameters were reported in all studies. The clinical characteristics reflect the population of interest (late preterm, term neonates, and infants), with a diversity of pathologies, but without sufficient details to further explore this.

Table 2 contains quantifications of the PK parameters stated in the publications kept to simplify comparison. Because each medication supplied during ECMO circulation has different features, the included studies, as shown in Table 2, were categorized by drug to simplify comparison.

Antimicrobials

Vancomycin

Almost consistent results were observed for vancomycin Cl, while findings on Vd were consistent between the 4 studies retrieved (Table 2). In the study of Cies et al.[18], the vancomycin Cl increased in the presence of ECMO, so that it was suggested to use a higher dose in these patients. The authors attributed this increased Cl to the specific ECMO circuit used. In all of these studies, the target range for vancomycin trough concentration was determined as greater than 10 mg/L[18], less than 15 mg/L[19 20] or 5-15 mg/mL[21]. In addition, in these 4 articles, the Vd of vancomycin increased in the presence of ECMO, be it not statistically significant in the individual studies.

In the Zylbersztajn[19] et al study, the PK/PD target was a ratio of >400 of the area under the curve to the minimum inhibitory concentration (AUC/MIC). Weight was also included as a covariate on both central Vd and Cl, and serum creatinine was also included on Cl for vancomycin. Furthermore, four vancomycin PK profiles met the lower PK/PD target, three of which corresponded to a dose of 15 mg/kg every 6 h. 63.6% of patients met the therapeutic achievement for sufficient exposure across all dosage intervals.

Moffett et al.[22] described the PK of vancomycin in paediatric patients undergoing ECMO and provide dosing recommendations. Serum creatinine level and postmenstrual age were significant factors for Cl, patient age for central Vd, and albumin for peripheral Vd in this investigation. Furthermore, the simulation indicated a dosage of 25-30 mg/kg/dose every 12-24 hours as having the largest percentage of individuals with an AUC for 24 hours larger than 400 and trough values less than 15 mg/L. Serum vancomycin concentration monitoring is recommended in paediatric patients undergoing ECMO circuits.

Meropenem

Because of the low meropenem adsorption in the ECMO circuit and the high dialysate rate in CRRT, the effects of ECMO and CRRT vary. This is mostly due to meropenem's chemical characteristics. According to the Wang et al.[23] study about a popPK model of meropenem in children with sepsis receiving extracorporeal life support, The PK characteristics of meropenem were not affected by ECMO intervention. Furthermore, ECMO and CRRT can raise Vd due to the extracorporeal circuits, although this study indicated that the impact on meropenem concentration was smaller than previously documented hemofilters. In summary, there was no significant changes in PK parameters were observed in children with

sepsis who were receiving ECMO. However, this study harbors some conspicuous limitations due to limited data and sample size. For this reason, we need more data on meropenem for children with sepsis undergoing ECMO circuit.

Zylbersztajn et al.[19] described primary PK/PD parameters of meropenem and vancomycin in paediatric patients undergoing ECMO. For meropenem, weight was added as a covariate on volume of the central compartment (Vc). To conclude, the authors suggested that maximal meropenem dose utilizing a prolonged infusion and at least current vancomycin dosing with therapeutic drug monitoring are required to achieve adequate PK/PD targets in this patient population (Table 3).

Fluconazole

The ECMO circuits can alter drug PK; therefore, standard fluconazole dosing may result in suboptimal drug exposures and efficacy. According to the Watt et al.[24] study, the fluconazole Vd was increased in neonates and infants supported by ECMO. Although the fluconazole Cl was not changed in neonates, it was increased in infants undergoing ECMO. As a result, children on ECMO who develop invasive candidiasis require a fluconazole loading dose of 35 mg/kg, followed by a daily maintenance dose of 12 mg/kg to achieve exposures comparable to those obtained in children who are not on ECMO and are loaded with 25 mg/kg and maintained on 12 mg/kg daily. However, children above the age of two are underrepresented in this study, and the findings should be generalized with caution to this demographic. As a result, confirmatory prospective clinical studies evaluating fluconazole exposure, safety, and effectiveness in this group are required (Table 4).

Gentamicin

Two articles examining the popPK of gentamicin in the presence of ECMO were reviewed. Dodge et al.[25] show that while undergoing ECMO, neonates have a higher Vd for gentamicin, a lower Cl, and a much longer $t_{1/2}$. Based on these findings, the required peak and trough plasma gentamicin concentrations for neonates receiving ECMO circuits (5-8 and 2 g/ml, respectively) were achieved. They recommended a loading dose of gentamicin (4.3 mg/kg) and a maintenance dose (3.7 mg/kg q18-24h) followed by monitoring of serum concentrations and appropriate dose adjustments thereafter. Moffett et al.[22] found that children had

elevated trough concentrations when gentamicin dosed according to standard dosing procedures. Therefore, fat-free mass should be used to dose gentamicin in patients undergoing ECMO circuit. Serum creatinine is also a marker of gentamicin clearance and should be used to change gentamicin dose in paediatric patients (Table 5). In all of these studies, the target range for gentamicin peak concentration was determined as approximately 6 mg/L.

Cefotaxime

Cefotaxime can be excreted unchanged or after hepatic conversion into its active metabolite via the renal system in adults. There may be an inverse correlation between renal function and elimination $t_{1/2}$, notably for desacetylcefotaxime as an active metabolite. According to the Ahsman et al.[26] study, the standard cefotaxime dosing regimen produces a high enough $t_{>MIC}$. The Vd was greater in ECMO patients than in non-ECMO patients (1.82 vs. 0.68 to 1.14 L), while cefotaxime Cl levels were similar. To effectively treat neonates undergoing ECMO, a dosage regimen of 50 mg/kg q12h (PNA, 1 week), 50 mg/kg q8h (PNA, 1 to 4 weeks), or 37.5 mg/kg q6h (PNA, >4 weeks) can be used (Table 6).

Cefepime

According to the current literature, the increase in peripheral Vd caused by blood transfusion is explained by the volume received than by the kind of fluids obtained. Also, cefepime is a hydrophilic drug with minimal protein binding, and fluid administration may improve its Vd. In the Thibault et al.[27] study, in paediatric patients undergoing ECMO, renal function was a key driver of cefepime Cl. Based on simulations, dosing regimens of 50mg/kg given every 8 hours resulted in optimum serum concentrations at a MIC of 8mg/L. Indeed, with lower MICs and greater serum creatinine levels, longer dose intervals were adequate (Table 7).

According to the Zuppa et al.[28] study, cefepime clearance was reduced compared with previously reported data in children not receiving ECMO.[29] Furthermore, the Vd of cefepime with the use of ECMO can increase about 2.5-fold compared with the volume without the use of ECMO, as a result, the total quantity of cefepime accessible for clearance is reduced. At the end of the study, it was concluded that only %74 doses revealed a *fT* MIC of 16 mg/L for more

than 70% of the dosing interval. As a result, cefepime TDM should be evaluated in the clinical setting to improve the ability to achieve therapeutic targets while limiting possible toxicity.

Sedatives & Analgesics

Midazolam

Two articles reported on midazolam PK in patients undergoing ECMO. Mulla et al.[30] reported that both the Vd and $t_{1/2}$ of midazolam increased. Clearance was 1.4 (SD 0.15) ml/kg/min, so that simulations with conventional doses resulted in excess levels. Altered PK may reflect sequestration of midazolam by components of the ECMO circuit. Besides, Ahsman et al.[31] reported an increased Vd and $t_{1/2}$, as well as a 3-fold increase in midazolam and 1-hydroxy-midazolam Cl in the first 5 days following ECMO initiation. Interestingly, concomitant inotropic infusion during ECMO increased 1-hydroxy-midazolam glucuronide Cl by 23%. They also determined the 1-hydroxy-midazolam/midazolam metabolic ratio (MR), a surrogate measure of cytochrome P450(CYP)3A activity, as being higher than previous reports in (pre)term neonates and attribute the reduced renal elimination Cl of the metabolite (Table 8).

Clonidine

Clonidine is used for sedation in the critically ill paediatric patients. However, clonidine during ECMO cannot be effectively titrated as PK parameter are lacking in neonates and infants. For this reason, Kleiber et al.[32] was aimed to describe clonidine PK in a particular ECMO system and propose dosing guidelines for children on this particular ECMO circuits. Clonidine Cl levels in children older than one month were double those found in patients not on ECMO. Furthermore, clearance rose sharply with postnatal age, reaching 30%, 50%, and 70% of the adult clearance rate at days 6, 8, and 10, respectively. During ECMO assistance, Vd rose by 55%. As a consequence, the maximum suggested bolus dosage was 5 g/kg, and the authors simulated the number of 5 g/kg bolus doses required to attain the goal concentration of 2 ng/ml within 1 h, and three repeated 5 g/kg bolus doses were required (Table 9).

Morphine

Two articles on the same population evaluating the PK of morphine and its metabolites in neonates undergoing ECMO were retained by the same authors.[33,17] In the first study,

morphine Cl was lower in neonates [postnatal age (PNA) 7 days] at the start of ECMO (2.2 l per hour per 70 kg) than in postoperative neonates (10.5 l per hour per 70 kg), but rapidly increased (maturation $t_{1/2}$ 30 and 70 days, respectively) to equal that of the postoperative group after 14 days. The authors stated that Cl was affected by size and age only and that Vd increased with age and was 2.5 times higher in neonates undergoing ECMO than in postoperative cases. Similar to the findings on phenobarbital, the coefficient of variation was significantly higher in neonates on ECMO when compared to postoperative cases.[17 34] Morphine-3-glucuronide (M3G) was the primary metabolite. In the study evaluating the PK of M3G, elimination Cl of M3G was lower in the neonates on ECMO, attributed to reduced renal elimination clearance. These elimination clearances were correlated positively with ECMO flow and negatively correlated with dopamine dose.[17] However, Peters et al. suggested that dopamine needs very likely is not causally associated with decreased clearance, but rather a reflection of poorer circulation[17] (Table 10).

Others

Phenobarbital

Body weight was the main PK covariate of phenobarbital disposition.[35] In the study by Michaličková et al., the Vd of phenobarbital was not much affected by ECMO, while its Cl increased over time, especially in the first 12 days.[34] Both (body weight and postnatal age) rather reflect maturational covariates. Furthermore, there was still high unexplained variability.[34] In both studies, the suggested target range for phenobarbital therapeutic concentration was 10-40 mg/L.

Thibault et al.[36] created a popPK model for IV phenobarbital in neonates following cardiac surgery and ran simulations to find the optimal dose regimes. Loading doses of 30 and 20 mg/kg reached target concentration with albumin levels less than or equal to 3 and 3.5 mg/dL, respectively, in neonates not on ECMO. Also, loading doses of 30 mg/kg were effective on ECMO independent of albumin levels. In addition, all neonates attained target concentrations with maintenance doses of 4-5 mg/kg/d. The purpose of this study was to assess the effect of changed protein binding or, more likely, positive fluid balance in phenobarbital dosing (Table 11).

Theophylline

According to the Mulla et al.[37] study that determined popPK for theophylline during ECMO from routine monitoring data, the estimated Cl is significantly lower, and Vd higher, than previously reported in non-ECMO patients of similar age. These variations are most likely due to the increased circulation volume during ECMO as well as decreased renal and hepatic function in this population. The high inter-individual variability reflects the varied character of ECMO patients (Table 12).

DISCUSSION

Most of the studies included in the review were on antimicrobials including vancomycin, meropenem, fluconazole, gentamicin, cefotaxim, and cefepim. This confirm the pattern on drug utilization described by Buck et al in 2003[9] both drugs are hydrophilic, have a rather low Vd (L/kg) and a narrow therapeutic range. Vd relates the amount of drug in the body to the plasma concentration of the drugs, depending on the fluid in which concentration is measured.[38] Vd depends on substance characteristics and patient factors which can be different between neonates and adults.

In this literature review, because drug clearance is difficult to predict because of dynamic ontogenetic changes in renal function, ECMO received neonates and infants without concomitantly CRRT included to avoid heterogeneity.[39] Therefore, target concentration intervention based on serum concentrations is indispensable to ensure therapeutic exposure in this population.

Most studies found that patients undergoing ECMO had higher Vd and lower Cl than non-ECMO patients. The PK differences in which we have the highest confidence are from trials that included non-ECMO comparison groups. However, the bulk of the studies, did not include non-ECMO comparator groups, and the comparisons were based on PK data provided in other published data.[40] The differences in Vd and Cl of some of the studied drugs, such as vancomycin, between ECMO and non-ECMO controls demonstrated significant intra-study variability, with some studies showing increased values for the PK parameters[31 32 36], while others showed decreased values or no change.[23 24 41]

In this literature review, most studies evaluated both VV and VA modalities of ECMO together. According to the Bhatt-Mehta et al.[42] study, there was no statistically significant between VA and VV bypass type in terms of Vd (0.61 ± 0.15 vs. 0.74 ± 0.23 L/kg), Cl (0.157 ± 0.046 vs. 0.199 ± 0.085 L/h), and $t_{1/2}$ (10.04 ± 2.45 vs. 10.75 ± 3.43 h) (p>0.05).[42] Therefore, it is estimated that none of the included studies analyzed the VV-VA difference in terms of PK parameters.

In general, changes in tissue distribution caused by a severe illness are more likely to be clinically important for hydrophilic drugs that lack meaningful intracellular penetration and so have a low Vd.[43] Also, because neonates have a larger proportion of body water, the Vd per kg for water-soluble substances may be higher.[44] In addition to all these factors, it is reasonable to expect that the Vd of hydrophilic drugs will increase once the ECMO circulation is connected. This can be attributed to the circuit itself, as well as to the additional capillary leak commonly observed in these patients. To further illustrate this, all studies examining vancomycin and gentamicin consistently showed an increased Vd in neonates undergoing ECMO.[8 9]

Phenobarbital is an anticonvulsant still commonly used in neonates and infants undergoing ECMO to treat seizures (18-20%) and withdrawal symptoms, with midazolam as a commonly used second-line drug to treat seizures or to sedate the newborn.[35] The distribution of phenobarbital, a lipophilic drug, was not affected by ECMO as the sodium salt formulation has good water solubility (logP= 1.77). In contrast, it was shown in two studies that the distribution of midazolam increased. Pokorná et al.[35] found similar high inter-individual PK variability for Vd and Cl and no statistical differences in Vd or Cl. The authors assumed that the physicochemical characteristics of phenobarbital resulted in differences in the distribution in comparison with ECMO-induced changes for typical lipophilic drugs. Michaličková et al.[34] found that the phenobarbital Cl increased in the time interval (day 1-12) studied within 12 days. Different loading and maintenance doses were used in both studies, and different Vd and Cl values were calculated. Because of the substantial unexplained variability, individual patients should consider regular and recurrent therapeutic drug monitoring and therapeutic concentration intervention, even with the model-derived regimen.[34]

Mulla et al.[30] have analyzed the PK of midazolam in neonates undergoing ECMO. Their midazolam model reveals a significantly altered Vd in ECMO patients, with a significant

prolongation of the $t_{1/2}$ (from 6.8 to 33.3 hours). Mulla et al.[30] did not report a correlation between Cl and duration of infusion or PNA. They also determined the MR, a surrogate measure of CYP3A activity, as being higher than previous reports in (pre)term neonates and attribute this to a reduced renal elimination Cl of the metabolite. Similarly, in the study of Ahsman et al.[31], it was shown that the Vd increased. But unlike Mulla et al.[30], they stated that Cl increased 3-fold within the first 5 days. It is estimated that this is due to the difference in the ECMO circuit construction (oxygenator). Ahsman et al.[31] also reported that concomitant inotropic infusion increased hydroxy-midazolam glucuronide Cl by 23% and midazolam dose could be increased starting from the 5th day.

Critical illness may significantly affect dexmedetomidine PK, mainly through decreased hepatic metabolism and elevated Vd induced by organ failure and inflammation, which may be modified further by the presence of ECMO. Increases in Cl result in higher dexmedetomidine concentrations, while increases in Vd result in lower concentrations. According to the Thibault et al.,[45] Exploration of PK data using previously published models resulted in overprediction of observed values, which might have theoretically suggested higher Vd and Cl. Adding a component on Vd, on the other hand, did not enhance their goodness of fit plots, implying that increasing Vd does not explain their findings. This study found that popPK models that are relevant to a wide range of ages and diseases are more feasible in paediatric critical care settings but more difficult to design.

Peters et al.[33] found that morphine Cl on ECMO lags behind that in healthy postoperative neonates of the same age but matures rapidly and was similar to the cohort of postoperative surgical neonates within two weeks. After this study, on the contrary, the same authors found that formation Cl to M3G is reduced during the first ten days of ECMO with the same study population.[17]

As a final reflection, we wanted to mention that we could not retrieve reports on any subsequent validation study for the adapted dosing regimens suggested. Furthermore, the reporting on toxicity and safety in these population PK studies is not present in these papers, so that additional studies to validate the adapted dosing regimens on efficacy and toxicity are warranted.[41] From a methodological perspective, better descriptions on the pathophysiology over time can be very useful to feed (patho)physiology-based PK models as illustrated for

fluconazole PK over the human age span, including neonates.[8 46] Previously, Hoie et al.[47] had recommended a vancomycin dose of 20 mg/kg at an 18-h interval for infants on ECMO with serum creatinine levels of <1.5 mg/dl. However, Amaker et al.[41] data indicate that infants on ECMO with serum creatinine levels of <1.5 mg/dl should be given vancomycin no more frequently than every 24 h. In comparison with previously published data, the neonates undergoing ECMO in this study demonstrated a much larger Vd, a lower Cl, and a longer $t_{1/2}$ with an individual PK study.

This paper has its strengths and limitations. The predefined approach to focus on population PK studies has limitations, but these methods does provide the best approach to analysis trends over time, as well as covariates involved. Furthermore, the search strategy was structured, but not compliant with all guidelines (like number of databases searched) relevant for a meta-analysis.

CONCLUSION

The aim of this paper was to determine the effect of ECMO use on PK in neonates, based on a systematic assessment of population PK studies. At present, there are a limited number of population PK studies for a limited number of compounds reported in neonates undergoing ECMO. Despite some differences in results for the same drug, the general pattern suggests an increase in Vd and $t_{1/2}$, a stable to decreased Cl, and an increase in intra- and interpatient variability on ECMO. There was no any relevant toxicity and safety parameters reported, including in those studies with more than 100% increased PK parameters. Therefore, we recommend more studies are needed to address this toxicity and safety concern. Consequently, and if possible, therapeutic drug monitoring and target concentration intervention are strongly recommended to determine the appropriate exposure and doses for neonates undergoing ECMO.

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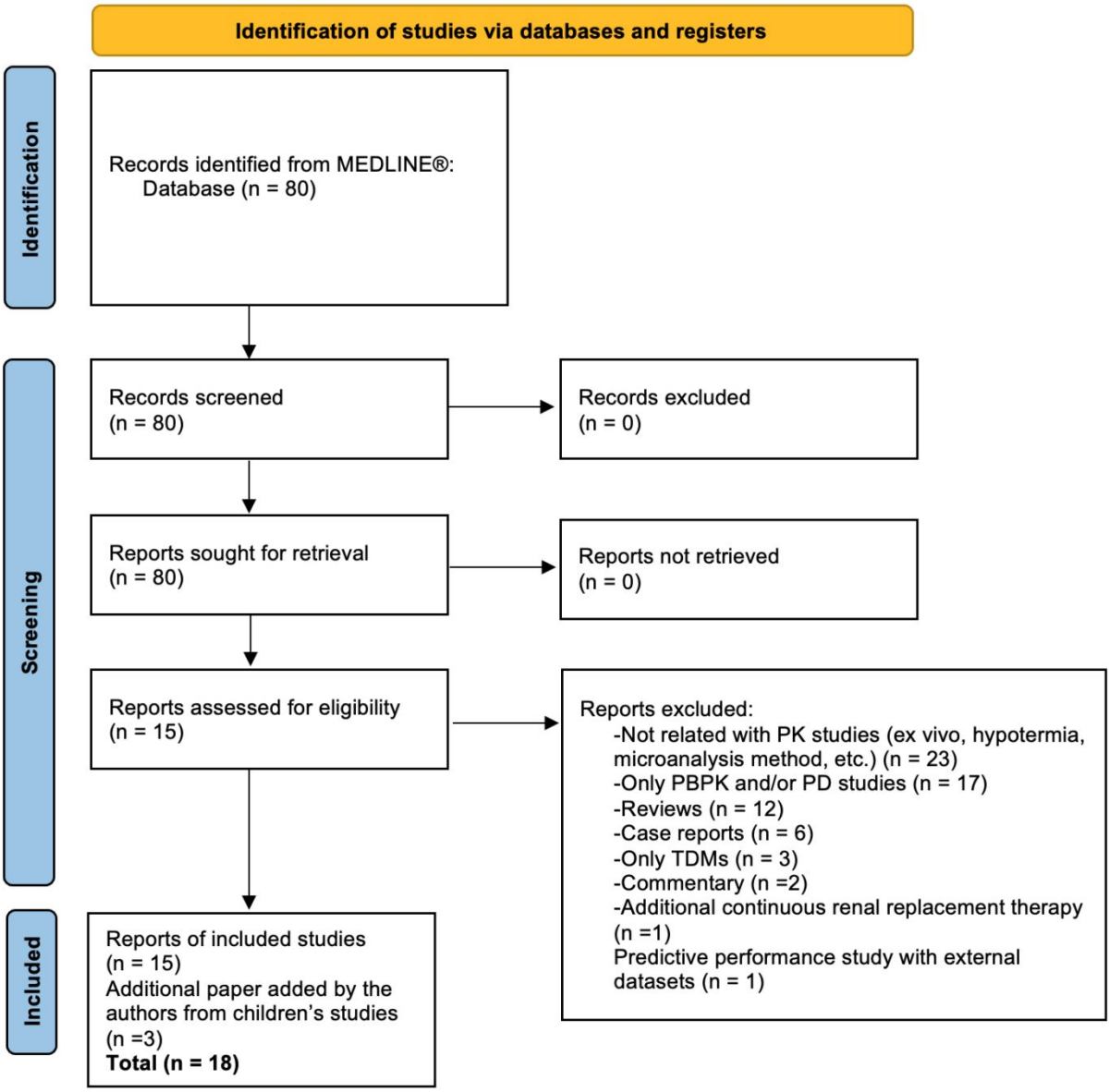
Figure 1. PRISMA flow diagram of data selection and subsequent results



MEDLINE: Medical Literature Analysis and Retrieval System Online, PK: Pharmacokinetics, PBPK: Physiologically based pharmacokinetic modelling, PD: Pharmacodynamics, TDM: Therapeutic drug monitoring

Table 1. Study characteristics (N=18)

Characteristics	**n**
Type of Study	
Prospective observational	11
Retrospective observational	6
Prospective & Retrospective	1
Drug	
Vancomycin	4
Meropenem	2
Fluconazol	1
Gentamicin	2
Cefepime	2
Midazolam	2
Phenobarbital	2
Theophylline	1
Clonidine	1
Morphine	1
Cefotaxime	1
ECMO Modality	
Veno-venous	-
Veno-arterial	2
Mixed	16
Pharmacokinetic Parameters	
Absorption	-
Distribution	16
Metabolic clearance	2
Renal clearence	17

Table 2. Characteristics of the studies, pharmacokinetics, and dose recommendations related to vancomycin

Study	n	PNA	Weight	Type	Group	Model	Modality	Administered Dose	V_d	C_L	$t_{1/2}$ (hours)	Recommended Dose
Mulla et al[21] 2005, UK	15	8.2	3.5	P&R	children	2-comp with WinNonMix	VV-VA	10–15mg/kg q6-24h	0.45 ± 0.1 L/kg	0.04± 0.02 L/kg/h	10.40 ±6.67	-
Cies et al[18] et al 2017, USA	12	9.5	3.1	R	neonates	1-comp with Pmetrics	VV-VA	10–15mg/kg q8-24h	1.2 ± 0.4 L/kg	3.48 ± 1.31 mL/min/kg	14.1 ± 6.9	-
Zylbersztajn et al[19] 2021, Chile		24 (2-132) months	10 (3.5-37)	P	children	2-comp with PMetrics	VV-VA	10-15 mg/kg q6-12h	0.419 ± 0.280 L/kg	0.060 ± 0.055 L/h/kg	-	Across each dosing interval 63.6% of patients achieved the PK/PD targets for adequate exposure.
Moffett et al[20] 2018, USA	N: 28 I: 28	0.64 (0.07-6.7) years	7.6 (3.7-21.9)	R	children	2-comp with NONMEM	VV-VA	25 mg/kg q18h for neonates 30 mg/kg q12h for infants	$Vd_{central}$: 0.36 L/kg $Vd_{peripheral}$: 0.462 L/kg -	0.942 mL/kg/min -	-	25–30 mg/kg/dose q12–24 h with serum concentration monitoring is a reasonable empiric dosing strategy to obtain an area under the curve for 24 h greater than 400.

N: Neonates, I: Infants, VV: Veno-venous, VA: veno-arterial, R: Retrospective, P: Prospective, LD: Loading dose, MD: Maintenance dose, CI: Continuous infusion
Boldface fonts represent comparisons to controls within the same study. In other studies, they represent comparisons to non-ECMO neonates from a different published study.

Table 3. Characteristics of the studies, pharmacokinetics, and dose recommendations related to meropenem

Study	n	PNA	Weight	Type	Group	Model	Modality	Administered Dose	V_d	C_L	$t_{1/2}$ (hours)	Recommended Dose
Wang et al[23] 2021, China	9*	2.00 (0.71-3.88) years	11.50 (9.50-36.30)	P	children	2-comp with first order Elimination with NONMEM	VV-VA	20-40 mg/kg q8h	-	11.59 (5.92–20.15) vs 13.51 (3.71-20.80) L/h **↓14.2%**	-	The authors recommended the opitimized dosing regimens for septic children receiving ECMO depending on the PTA of PK target 50%T > MIC and 100%T > MIC, for children with sepsis during ECMO with different body weight, estimated Cl and MIC of bacteria.
Zylbersztajn et al.[19] 2021, Chile	9	48 (2–165) months	16 (3.5–45)	P	children	2-comp with PMetrics	VV-VA	20-40 mg/kg q8-12h	0.289 ± 0.295 L/kg **-**	0.139 ± 0.102 L/h/kg -	-	Across each dosing interval 91% of patients achieved the PK/PD targets for adequate exposure for meropenem. Higher dosing with extended infusion were needed in the meropenem administration.

VV: Veno-venous, VA: veno-arterial, R: Retrospective, P: Prospective, LD: Loading dose, MD: Maintenance dose, CI: Continuous infusion, PTA: probability of target attainment, MIC: minimum inhibitor concentration
Boldface fonts represent comparisons to controls within the same study. In other studies, they represent comparisons to non-ECMO neonates from a different published study.
*Number of patients undergoing only ECMO circuit.

Table 4. Characteristics of the studies, pharmacokinetics, and dose recommendations of isolated studies on fluconazole

Study	n	PNA	Weight	Study design	Group	Model	Modality	Administered Dose	V_d	Cl	$t_{1/2}$ (hours)	Recommended Dose
Watt et al[24] *2015, USA*	40	22	3.4	P 2-groups	infants	1-comp. with NONMEM	VV	25 mg/kg loading dose followed 12 mg/kg/day maintenance therapy	For neonates (ECMO vs. non-ECMO): 1.5 (1.3, 1.8) vs. 0.96 (0.55, 1.4) L/kg **↑56.2%** For infants (ECMO vs. non-ECMO): 1.2 (0.91, 1.6) vs. 0.83 (0.72, 1.0) L/kg **↑44.6%**	For neonates (ECMO vs. non-ECMO): 0.018 (0.013, 0.045) vs. 0.018 (0.008, 0.042) L/h/kg **↔** For infants (ECMO vs. non-ECMO): 0.022 (0.011, 0.035) vs. 0.017 (0.008, 0.026) L/h/kg **↑29.4%**	-	12 mg/kg for prophylaxis 35 mg/kg for invasive candidiasis treatment

VV: Veno-venous, VA: veno-arterial, R: Retrospective, P: Prospective, NONMEM: Nonlinear mixed-effects modelling, LD: Loading dose, MD: Maintenance dose, CI: continuous infusion6
Boldface fonts represent comparisons to controls within the same study. In other studies, they represent comparisons to non-ECMO neonates from a different published study

Table 5. Characteristics of the studies, pharmacokinetics, and dose recommendations related to gentamicin

Study	n	PNA	Weight	Study design	Group	Model	Modality	Administered Dose	V_d	Cl	$t_{1/2}$ (hours)	Recommended Dose
Dodge et al 1994, USA[25]	11	37-42 PMA	2.67-5.10	P 1-group	Neonates and infants	1-comp with NPEM	VV-VA	2.5 mg/kg loading dose and q8-12h maintenance dose	From 0.748 L/kg to 0.471 L/kg after ECMO was discontinued **↑58.8%**	From 0.239 L/h to 0.350 L/h after ECMO was discontinued **↓31.2%**	From 9.24 h to 3.87 h after ECMO was discontinued **↑138.7%**	4.3 mg/kg loading dose 3.7 mg/kg q18-24h maintenance dose
Moffett et al 2018, USA[22]	N: 28 I:5	0.17 (0.12 - 0.82) m	3.1 (2.4-3.8)	R 1-group	Mostly neonates and infants	2-comp with NONMEM	VV-VA	1.8 mg/kg/dose	0.60 L/kg -	0.03 L/kg/h	-	Children with elevated serum creatinine values should have extended dosing intervals (4-5 mg(kg/day).

N: Neonates, I: Infants, VV: Veno-venous, VA: veno-arterial, R: Retrospective, P: Prospective, NPEM: Nonparametric expectation and maximization, LD: Loading dose, MD: Maintenance dose, CI: Continuous infusion
Boldface fonts represent comparisons to controls within the same study. In other studies, they represent comparisons to non-ECMO neonates from a different published study.

Table 6. Characteristics of the studies, pharmacokinetics, and dose recommendations of isolated studies on cefotaxime

Study	n	PNA	Weight	Study design	Group	Model	Modality	Administered Dose	V_d	C_L	$t_{1/2}$ (hours)	Recommended Dose
Ahsman et al[26] 2010, the Netherlands	37	3.3 (0.67-199)	3.5 (2.0-6.2)	P 1-group	neonates	1-comp. with NONMEM	VV-VA	50 mg/kg q12h (PNA<1 w) 50 mg/kg q8h (1<PNA<4 w) 37.5 mg/kg q6h (PNA>4 w)	ECMO vs. non-ECMO: 1.82 L vs. 0.68 to 1.14 L **↑59.6-167.6%**	ECMO vs. non-ECMO: 0.36 L/h vs 0.20 to 0.55 L/h ↔	3.5 h	The standard cefotaxime dose regimen provides a sufficiently high $t_{>MIC}$ in infants undergoing ECMO.

IQR: Interquartile range, VV: Veno-venous, VA: veno-arterial, R: Retrospective, P: Prospective, NONMEM: Nonlinear mixed-effects modelling, LD: Loading dose, MD: Maintenance dose, CI: Continuous infusion, MIC: Minimum inhibitor concentration

Boldface fonts represent comparisons to controls within the same study. In other studies, they represent comparisons to non-ECMO neonates from a different published study

Table 7. Characteristics of the studies, pharmacokinetics, and dose recommendations of isolated studies on cefepime

Study	n	PNA	Weight	Study design	Group	Model	Modality	Administered Dose	V_d	CL	$t_{1/2}$ (hours)	Recommended Dose
Thibault et al[27] *2022, USA*	9/17	0.5 (0.2-2.5) m	4.4 (3.5-4.6)	P 1-group	Children	2-comp. with NONMEM	VV-VA	50 mg/kg q6-24h or 100-150 mg/kg/d continuous infusion	Vc + Vp = 0.6 L/kg	410 ml/h/4.4 kg	-	Dosing regimens of 50mg/kg q8h reached optimal concentrations at an MIC of 8mg/L based on simulations.
Zuppa et al[28] *2019, USA*	17	1.3-22 m	3.3-10	P 1-group	infants	2-comp with NONMEM	VV-VA	50 mg/kg q8-24h	Vc + Vp = 0.4 L/kg **↑250%**	7.1mL/min/3.8 kg **↓26.6%**	-	For free cefepime, only 14 of the 19 doses (74%) demonstrated a *fT*_MIC of 16 mg/L, an appropriate target for the treatment of *pseudomonal* infections, for greater than 70% of the dosing interval.

IQR: Interquartile range, VV: Veno-venous, VA: veno-arterial, R: Retrospective, P: Prospective, NONMEM: Nonlinear mixed-effects modelling, LD: Loading dose, MD: Maintenance dose, CI: Continuous infusion, MIC: Minimum inhibitor concentration

Boldface fonts represent comparisons to controls within the same study. In other studies, they represent comparisons to non-ECMO neonates from a different published study

Table 8. Characteristics of the studies, pharmacokinetics, and dose recommendations related to midazolam

Study	n	PNA	Weight	Study design	Group	Model	Modality	Administered Dose	V_d	C_L	$t_{1/2}$ (hours)	Recommended Dose
Mulla et al 2003, UK[30]	19	3.8	3.4	P Random 2-groups	neonates	1-comp. with WinNonMix	VV-VA	50-250 μg /kg/h	From 0.8±0.5 to 4.1±0.5 L/kg **↑412.5%**	1.4 ± 015 mL/kg -	From 6.8 (2.2–39.8) to 33.3 (7.4-178) **↑389.7%**	LD: 350 μg /kg/h for 6 hours MD: 50 μg /kg/h
Ahsman et al[31] *et al 2010, the Netherlands*	20	0.79	3.0	P 1-group	neonates	A two-compartment model for midazolam and a one-compartment model for the metabolites with NONMEM	VA	LD: 0.2 mg/kg bolus MD: 0.1 mg/kg/h CI	Midazolam: 14.6 L/3kg 1-hydroxymidazolam: 10.2 L/3 kg Hydroxymidazolam glucuronide: 1.21 L/3 kg **↑240.3%**	Midazolam: 1.38 L/h/3 kg 1-hydroxymidazolam: 1.03 L/h/3 kg Hydroxymidazolam glucuronide: 0.18 L/h/3 kg **↑300.0%**	1.85 -	LD: 300 μg /kg/h for 6 hours MD: 150 μg /kg/h

VV: Veno-venous, VA: veno-arterial, R: Retrospective, P: Prospective, NONMEM: Nonlinear mixed-effects modelling, LD: Loading dose, MD: Maintenance dose, CI: Continuous infusion
Boldface fonts represent comparisons to controls within the same study. In other studies, they represent comparisons to non-ECMO neonates from a different published study.

Table 9. Characteristics of the studies, pharmacokinetics, and dose recommendations of isolated studies on clonidine

Study	n	PNA	Weight	Study design	Group	Model	Modality	Administered Dose	V_d	C_L	$t_{1/2}$ (hours)	Recommended Dose
Kleiber et al[32] 2017, the Netherlands	22	1 (IQR 6.4) m	4 (IQR 3.1)	P 2-groups	Children	1-comp. with NONMEM	VV-VA	0.24 (0.15) µg/kg/h infusion	454 L/70 kg at ECMO start **↑55%**	29.9 L/h/70 kg at ECMO start **↑200%**	-	The authors simulated the number of bolus doses of 5 µg/kg needed to reach the target concentration of 2 ng/ml within 1 h: three repeated bolus doses of 5 µg/kg were needed.

IQR: Interquartile range, VV: Veno-venous, VA: veno-arterial, R: Retrospective, P: Prospective, NONMEM: Nonlinear mixed-effects modelling, LD: Loading dose, MD: Maintenance dose, CI: Continuous infusion6
Boldface fonts represent comparisons to controls within the same study. In other studies, they represent comparisons to non-ECMO neonates from a different published study

Table 10. Characteristics of the studies, pharmacokinetics, and dose recommendations of isolated studies on morphine

Study	n	PNA	Weight	Study design	Group	Model	Modality	Administered Dose	V_d	Cl	$t_{1/2}$ (hours)	Recommended Dose
Peters et al[33] 2005, the Netherlands	14	82	4.2	P	infants	1-comp. with NONMEM	VA	LD: 100 µg /kg MD: 40 µg /kg/h	Day 1: 1.89 mL/kg/min Day 10: 3.33 mL/kg/min **↑76.2%**	Day 1: 1.1 mL/kg/min Day 10: 6.0 mL/kg/min **↑445.5%**	-	Serum concentrations decrease during the first 10 days of ECMO, and that dose adjustments should be carried out.

VV: Veno-venous, VA: veno-arterial, R: Retrospective, P: Prospective, LD: Loading dose, MD: Maintenance dose, CI: Continuous infusion6
Boldface fonts represent comparisons to controls within the same study. In other studies, they represent comparisons to non-ECMO neonates from a different published study

Table 11. Characteristics of the studies, pharmacokinetics, and dose recommendations related to phenobarbital

Study	n	PNA	Weight	Type	Group	Model	Modality	Administered Dose	V_d	C_L	$t_{1/2}$ (hours)	Recommended Dose
Michaličková et al[34] et al 2020, Czech Republic	13	2	3.21	R	neonates	1-comp with NONMEM	VV-VA	LD: 7.5mg/kg (8.5–16mg/kg) MD: 6.9mg/kg/d (4.5–8.5 mg/kg/d).	2.72 L	0.0096 L/h	-	In the first 12 days of ECMO with a regimen of a LD of 20 mg/kg and a MD of 4 mg/kg/d divided in two doses with an increase of 0.25 mg/kg every 12 hours during ECMO
Thibault et al[36] 2020, USA	12/37*	5 (0-26)	3.2 (1.3-3.8)	R	neonates	1-comp with first-order elimination with NONMEM	VV-VA	LD: 15-20 mg/kg MD: 3-6 mg/kg/d	**↑22%** (Normalization of albumin values from 2.5 mg/dL to 3.5 mg/dL decreased the estimated V by 13%)	**↑114%** (Over the first 20 days of life)	-	LD 30 mg/kg achieved goal peak concentration. MD of 4-5 mg/kg/d sustained goal trough concentration

VV: Veno-venous, VA: veno-arterial, R: Retrospective, P: Prospective, LD: Loading dose, MD: Maintenance dose, CI: Continuous infusion
Boldface fonts represent comparisons to controls within the same study. In other studies, they represent comparisons to non-ECMO neonates from a different published study.
*Number of patients undergoing only ECMO circuit.

Table 12. Characteristics of the studies, pharmacokinetics, and dose recommendations related to theophylline

Study	n	PNA	Weight	Study design	Group	Model	Modality	Administered Dose	V_d	C_L	$t_{1/2}$ (hours)	Recommended Dose
Mulla et al[37] 2003, UK	N: 38 I: 14	8.4 ± 5.9 for neonates 122 ± 107 for infants	3.3 ± 0.5 for neonates 4.8 ± 2.0 for infants	R 1-group compared with the literature	Children	1-comp. with first order elimination with Win-NonMix Professional	VV-VA	9.2 ± 2.6 µg/kg/min infusion	The interindividual variability **↑40%**	The interindividual variability **↓38%**	-	Maintenance infusion rates following an initial loading dose (0.57 x weight (kg) x 10 mg/L). Maintenance infusion rate calculated from: average steady-state concentration = rate of infusion/clearance (using clearance parameters determined in the final model).

N: Neonates, I: Infants, VV: Veno-venous, VA: veno-arterial, R: Retrospective, P: Prospective, NONMEM: Nonlinear mixed-effects modelling, LD: Loading dose, MD: Maintenance dose, CI: Continuous infusion6
Boldface fonts represent comparisons to controls within the same study. In other studies, they represent comparisons to non-ECMO neonates from a different published study

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Population Pharmacokinetics in Critically Ill Neonates and Infants Undergoing Extracorporeal Membrane Oxygenation: A Literature Review

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Abstract

Extracorporeal membrane oxygenation (ECMO) increases circulating blood volume, capillary leak, and temporarily alters kidney function. Consequently, pharmacokinetics (PK) can be affected. When applied to neonates and infants, additional dose adjustments are a major concern, as the volume of distribution (Vd) is already generally greater for water-soluble drugs and the clearance (Cl) of drugs eliminated by glomerular filtration is reduced. A systematic search was performed on MEDLINE® (1994-2022) using a combination of the following search terms: "pharmacokinetics", "extracorporeal membrane oxygenation", and "infant, newborn" using MeSH search strategy. Nine out of 18 studies on 11 different drugs (vancomycin, meropenem, fluconazole, gentamicin, midazolam, phenobarbital, theophylline, clonidine, morphine, cefotaxime, and cefepime) recommended dose increase/decrease by determining PK parameters. In other studies, it has been suggested to adjust the dose intervals. While the $t_{1/2}$ and Vd mostly increased for all drugs, the Cl of the drugs has been shown to be variability except for midazolam and morphine. There are a limited number of population PK studies in neonates and infants undergoing ECMO circuits. Despite some divergences, the general pattern suggests an increase in Vd and $t_{1/2}$, an increased, stable or decreased Cl, and an increase in variability. Consequently, and if possible, therapeutic drug monitoring and target concentration intervention are strongly recommended to determine appropriate exposure and doses for neonates and infants undergoing ECMO support.

Keywords: neonates; infants; pharmacokinetics; ECMO; antimicrobials; anticonvulsants; sedo-analgesics

Key messages

- An increase in volume of distrubition (Vd), with still high inter- and intraindividual variability in PK parameters of many drugs in ECMO cohorts is observed.
- Therapeutic drug monitoring and target concentration intervention are strongly recommended to determine appropriate exposure and doses for neonates and infants undergoing ECMO.
- There have been very few studies of the effect of ECMO on population PK data for 11 different drugs (vancomycin, meropenem, fluconazol, gentamicin, midazolam, phenobarbital, theophylline, clonidine, morphine, cefotaxime, and cefepime) in neonates and infants.

INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) is a cardiopulmonary bypass procedure used to provide temporary respiratory or cardiac support to critically ill patients, including neonates and infants.[1 2] ECMO has two cannulation techniques: veno-venous (VV) and veno-arterial (VA). Veno-venous ECMO is mainly used for patients with respiratory failure, while veno-arterial ECMO support is rather used in patients with cardiac failure.[3 4]

While polypharmacy is well recognized in hospitalized adults, it is also quite common in hospitalized neonates and infants in intensive care units (ICU). Because survival and overall outcome rely on medicines, effective drug therapy is essential to improve care and minimize adverse effects.[5 6] This includes targeted dosing and exposure, but necessitates understanding and data on pharmacokinetic (PK) changes related to ECMO use in this specific population of neonates.

Volume of distribution (Vd), which specifies the dosage necessary to generate the desired peak concentration, and clearance (Cl), which is the volume of fluid cleared of drug from the body per unit of time, are the fundamental drivers of drug pharmacokinetics (PK). Vd and Cl are also important drivers of elimination half-life ($t_{1/2}$). The $t_{1/2}$ can be calculated with the following simple formula:

- $t_{1/2} = 0.693 * Vd/Cl$

Although an approximate, from a clinical point of view, this formula relates $t_{½}$ to Vd, CL, and steady-state, which represent the basic PK parameters.[7]

Understanding the parameters impacting medication PK and PD in the complicated setting of patient immaturity, severe illness, (multi)organ failure, and the necessity for supportive extracorporeal circuits is crucial for safe and successful prescription in neonates and infants undergoing ECMO.[8] Many medications' PK can be impacted by ECMO since it raises circulating blood volume, causes capillary leak, and temporarily affects renal function.

The underlying mechanisms related to the additional (non)-maturational changes in PK during ECMO are diverse, and in part related to the ECMO equipment, the impact of the technique, and the medical condition of the neonates and infants.[9] The ECMO equipment alters drug

exposure through adsorption by circuit components. This is to a certain extent drug-specific, and is more pronounced for drugs with high lipophylicity.[10] The need for ECMO will results in shift in fluid balance, capillary leak, and also in renal impairment; Acute kidney injury (AKI) is common in ECMO or cardiac bypass cases.[8 11 12] Finally, the medical condition like sepsis, or cardiac failure in itself will affect PK.[13] These non-maturational factors add on to the maturational PK of many drugs in neonates, different from those in adults.

All of these PK parameters (absorption, distribution, metabolism, and elimination, or ADME) exhibit maturation (age or weight-dependent alterations), but they are also influenced by non-maturational variables (disease, treatment, co-medications, environment or genetic background).[13] The Vd in neonates is usually larger for water-soluble drugs. Therefore, the Vd is generally increased, whereas Cl is decreased in neonates undergoing ECMO, especially for drugs cleared by renal route.[10-12] There are some variations in the Vd due to body composition, blood flow, protein binding, and membrane permeability.[14] Because renal clearance of metabolites is decreased in preterm and term infants, active metabolites may accumulate.[15]

According to the current literature, we aware that many pharmacological treatments in neonates and infants undergoing ECMO have not been fully studied and the risk-benefit ratios are not clearly defined. The aim of this literature review is therefore to provide an overview of the effects of ECMO on drug PK parameters in neonates (postnatal age 0-28 days) and infants (birth to 1-year old), specifically clearance, Vd, $t_{1/2}$ with recommended doses.

METHODS

A systematic literature search was performed on MEDLINE® (National Library of Medicine PubMed) of all literature between January 1994 and February 2022 in the PubMed database in September 2022. The search was made using of following keywords "pharmacokinetics", "extracorporeal membrane oxygenation", "infant, newborn". In MEDLINE® the corresponding MeSH search strategy for these search terms as the main heading (descriptor) were used.[16] 'AND' was used to separate the main search terms. Papers meeting the following criteria were accepted for the study:

- Full-text written in English,
- Concerned the human species,

- Research articles (clinical study, comparative study, multicenter study, observational study etc.),
- The reporting of a PK parameter for at least one of the absorption, distribution, metabolism, or excretion (ADME) process,
- Full-text is available,
- The references and citations of the retained papers were checked (backward snowball method),
- If necessary, additional paper added by the authors.

Articles were excluded if the study population did not include neonates/infants, or if only ECMO (like e.g., concomitant continuous renal replacement therapy (CRTT)) was not applied. Also, case reports, case series, reviews, commentaries, and guidelines were excluded, as we only focused on population pharmacokinetic studies. Physiologically based pharmacokinetics and TDM studies were excluded. Full-texts for all papers were retrieved through various research databases.

First, the titles of all articles were screened. If the relevance was unsure, the abstract was subsequently read. Finally, the resulting selected articles were thoroughly studied, and the references were screened for secondary inclusion after both authors (NS and NY) reach a consensus. All references and citations to the included articles verificated, and no additional studies were identified to be included. Furthermore, an additional search was performed by the authors using the keywords "pharmacokinetics", "extracorporeal membrane oxygenation" and "paediatrics" from MeSH search terms to identify studies with the paediatric population that included newborn and/or infant patients undergoing ECMO circuit.

Patient and public involvement

This study was done without the participation of patients or parents. Patients or parents were not invited to comment on the trial design, nor were they contacted to define patient-relevant outcomes or interpret the findings. Patients or parents were not asked to help write or revise this text for readability or accuracy.

RESULTS

In this search, in total 16 papers were retained with the keyword's "pharmacokinetics", "extracorporeal membrane oxygenation", "infant, newborn". One article related morphine metabolite was excluded because it was a follow-up to another article with the same study protocol and population.[17] There are also 3 additional papers from 135 results added by the authors from children's studies including newborns and/or infants' data. In this manner, the literature review was completed with a total of 18 papers. The articles were published in the MEDLINE® database starting in 1994 (1 report before 2000, 4 between 2000-2009, 7 between 2010-2019, and already 6 reports from 2020 onwards), with a variety of nations participating (depending on the corresponding author). There were no additional articles were found matching the inclusion criteria with the backward snowball method. A flow diagram of data selection, reasons for exclusion, and subsequent results are provided in Figure 1.

Characteristics of included studies (n=18) are provided in Table 1. One of the included studies was both prospective and retrospective. Most of the drugs studied are antibiotics (vancomycin, meropenem, fluconazole, and gentamicin), followed by midazolam and phenobarbital. The route of administration was intravenous in all studies. Therefore, enteral absorption was not evaluated. Studies were limited to the mother compounds, except for data on the PK parameters of midazolam and morphine metabolites. Vd and Cl parameters were reported in all studies. The clinical characteristics reflect the population of interest (late preterm, term neonates, and infants), with a diversity of pathologies, but without sufficient details to further explore this.

Antimicrobials

Vancomycin

Similar results were observed for vancomycin Cl, while findings on Vd were consistent between the 4 studies retrieved (Table 2). In all of these studies, it was observed that while Cl decreased, Vd increased for the patients undergoing ECMO circuits. In the study of Cies et al.[18], the vancomycin Cl increased in the presence of ECMO, so that it was suggested to use a higher dose in these patients. The authors attributed this increased Cl to the specific ECMO circuit used. In all of these studies, the target range for vancomycin trough concentration was

determined as greater than 10 mg/L[18], less than 15 mg/L[19 20] or 5-15 mg/L[21]. In addition, in these 4 articles, the Vd of vancomycin increased in the presence of ECMO, be it not statistically significant in the individual studies.

In the Zylbersztajn[19] et al study, the PK/PD target was a ratio of >400 of the area under the curve to the minimum inhibitory concentration (AUC/MIC). Weight was also included as a covariate on both central Vd and Cl, and serum creatinine was also included on Cl for vancomycin. Furthermore, four vancomycin PK profiles met the lower PK/PD target, three of which corresponded to a dose of 15 mg/kg every 6 h. 63.6% of patients met the therapeutic achievement for sufficient exposure across all dosage intervals.

Moffett et al.[22] described the PK of vancomycin in paediatric patients undergoing ECMO and provide dosing recommendations. Serum creatinine level and postmenstrual age were significant factors for Cl, patient age for central Vd, and albumin for peripheral Vd in this investigation. Furthermore, the simulation indicated a dosage of 25-30 mg/kg/dose every 12-24 hours as having the largest percentage of individuals with an AUC for 24 hours larger than 400 and trough values less than 15 mg/L. Serum vancomycin concentration monitoring is recommended in paediatric patients undergoing ECMO circuits.

Meropenem

Two studies looked at meropenem (Table 3). Because of the low meropenem adsorption in the ECMO circuit and the high dialysate rate in CRRT, the effects of ECMO and CRRT vary. This is mostly due to meropenem's chemical characteristics. According to the Wang et al.[23] study about a popPK model of meropenem in children with sepsis receiving extracorporeal life support, The PK characteristics of meropenem were not affected by ECMO intervention. Furthermore, ECMO and CRRT can raise Vd due to the extracorporeal circuits, although this study indicated that the impact on meropenem concentration was smaller than previously documented hemofilters. In summary, there was no significant changes in PK parameters were observed in children with sepsis who were receiving ECMO. However, this study harbors some conspicuous limitations due to limited data and sample size. For this reason, we need more data on meropenem for children with sepsis undergoing ECMO circuit.

Zylbersztajn et al.[19] described primary PK/PD parameters of meropenem and vancomycin in paediatric patients undergoing ECMO. For meropenem, weight was added as a covariate on volume of the central compartment (Vc). To conclude, the authors suggested that maximal meropenem dose utilizing a prolonged infusion and at least current vancomycin dosing with therapeutic drug monitoring are required to achieve adequate PK/PD targets in this patient population (Table 3).

Fluconazole

The ECMO circuits can alter drug PK; therefore, standard fluconazole dosing may result in suboptimal drug exposures and efficacy. According to the Watt et al.[24] study, the fluconazole Vd was increased in neonates and infants supported by ECMO. Although the fluconazole Cl was not changed in neonates, it was increased in infants undergoing ECMO. As a result, children on ECMO who develop invasive candidiasis require a fluconazole loading dose of 35 mg/kg, followed by a daily maintenance dose of 12 mg/kg to achieve exposures comparable to those obtained in children who are not on ECMO and are loaded with 25 mg/kg and maintained on 12 mg/kg daily. However, children above the age of two are underrepresented in this study, and the findings should be generalized with caution to this demographic. As a result, confirmatory prospective clinical studies evaluating fluconazole exposure, safety, and effectiveness in this group are required (Table 4).

Gentamicin

Two articles examining the popPK of gentamicin in the presence of ECMO were reviewed. Dodge et al.[25] show that while undergoing ECMO, neonates have a higher Vd for gentamicin, a lower Cl, and a much longer $t_{1/2}$. Based on these findings, the required peak and trough plasma gentamicin concentrations for neonates receiving ECMO circuits (5-8 and 2 g/ml, respectively) were achieved. They recommended a loading dose of gentamicin (4.3 mg/kg) and a maintenance dose (3.7 mg/kg q18-24h) followed by monitoring of serum concentrations and appropriate dose adjustments thereafter. Moffett et al.[22] found that children had elevated trough concentrations when gentamicin dosed according to standard dosing procedures. Therefore, fat-free mass should be used to dose gentamicin in patients undergoing ECMO circuit. Serum creatinine is also a marker of gentamicin clearance and should be used to change gentamicin dose in paediatric patients (Table 5). In all of these

studies, the target range for gentamicin peak concentration was determined as approximately 6 mg/L.

Cefotaxime

Cefotaxime can be excreted unchanged or after hepatic conversion into its active metabolite via the renal system in adults. There may be an inverse correlation between renal function and elimination $t_{1/2}$, notably for desacetylcefotaxime as an active metabolite. According to the Ahsman et al.[26] study, the standard cefotaxime dosing regimen produces a high enough $t_{>MIC}$. The Vd was greater in ECMO patients than in non-ECMO patients (1.82 vs. 0.68 to 1.14 L), while cefotaxime Cl levels were similar. To effectively treat neonates undergoing ECMO, a dosage regimen of 50 mg/kg q12h (PNA, 1 week), 50 mg/kg q8h (PNA, 1 to 4 weeks), or 37.5 mg/kg q6h (PNA, >4 weeks) can be used (Table 6).

Cefepime

According to the current literature, the increase in peripheral Vd caused by blood transfusion is explained by the volume received than by the kind of fluids obtained. Also, cefepime is a hydrophilic drug with minimal protein binding, and fluid administration may improve its Vd. In the Thibault et al.[27] study, in paediatric patients undergoing ECMO, renal function was a key driver of cefepime Cl. Based on simulations, dosing regimens of 50mg/kg given every 8 hours resulted in optimum serum concentrations at a MIC of 8mg/L. Indeed, with lower MICs and greater serum creatinine levels, longer dose intervals were adequate (Table 7).

According to the Zuppa et al.[28] study, cefepime clearance was reduced compared with previously reported data in children not receiving ECMO.[29] Furthermore, the Vd of cefepime with the use of ECMO can increase about 2.5-fold compared with the volume without the use of ECMO, as a result, the total quantity of cefepime accessible for clearance is reduced. At the end of the study, it was concluded that only %74 doses revealed a *fT* MIC of 16 mg/L for more than 70% of the dosing interval. As a result, cefepime TDM should be evaluated in the clinical setting to improve the ability to achieve therapeutic targets while limiting possible toxicity.

Sedatives & Analgesics

Midazolam

Two articles reported on midazolam PK in patients undergoing ECMO. Mulla et al.[30] reported that both the Vd and $t_{1/2}$ of midazolam increased. Clearance was 1.4 (SD 0.15) ml/kg/min, so that simulations with conventional doses resulted in excess levels. Altered PK may reflect sequestration of midazolam by components of the ECMO circuit. Besides, Ahsman et al.[31] reported an increased Vd and $t_{1/2}$, as well as a 3-fold increase in midazolam and 1-hydroxy-midazolam Cl in the first 5 days following ECMO initiation. Interestingly, concomitant inotropic infusion during ECMO increased 1-hydroxy-midazolam glucuronide Cl by 23%. They also determined the 1-hydroxy-midazolam/midazolam metabolic ratio (MR), a surrogate measure of cytochrome P450(CYP)3A activity, as being higher than previous reports in (pre)term neonates and attribute the reduced renal elimination Cl of the metabolite (Table 8).

Clonidine

Clonidine is used for sedation in the critically ill paediatric patients. However, clonidine during ECMO cannot be effectively titrated as PK parameter are lacking in neonates and infants. For this reason, Kleiber et al.[32] was aimed to describe clonidine PK in a particular ECMO system and propose dosing guidelines for children on this particular ECMO circuits. Clonidine Cl levels in children older than one month were double those found in patients not on ECMO. Furthermore, clearance rose sharply with postnatal age, reaching 30%, 50%, and 70% of the adult clearance rate at days 6, 8, and 10, respectively. During ECMO assistance, Vd rose by 55%. As a consequence, the maximum suggested bolus dosage was 5 g/kg, and the authors simulated the number of 5 g/kg bolus doses required to attain the goal concentration of 2 ng/ml within 1 h, and three repeated 5 g/kg bolus doses were required (Table 9).

Morphine

Two articles on the same population evaluating the PK of morphine and its metabolites in neonates undergoing ECMO were retained by the same authors.[33,17] In the first study, morphine Cl was lower in neonates [postnatal age (PNA) 7 days] at the start of ECMO (2.2 l per hour per 70 kg) than in postoperative neonates (10.5 l per hour per 70 kg), but rapidly increased (maturation $t_{1/2}$ 30 and 70 days, respectively) to equal that of the postoperative group after 14 days. The authors stated that Cl was affected by size and age only and that Vd increased with age and was 2.5 times higher in neonates undergoing ECMO than in postoperative cases. Similar to the findings on phenobarbital, the coefficient of variation was

significantly higher in neonates on ECMO when compared to postoperative cases.[17 34] Morphine-3-glucuronide (M3G) was the primary metabolite. In the study evaluating the PK of M3G, elimination Cl of M3G was lower in the neonates on ECMO, attributed to reduced renal elimination clearance. These elimination clearances were correlated positively with ECMO flow and negatively correlated with dopamine dose.[17] However, Peters et al. suggested that dopamine needs very likely is not causally associated with decreased clearance, but rather a reflection of poorer circulation[17] (Table 10).

Others

Phenobarbital

Phenobarbital is an anticonvulsant still commonly used in neonates and infants undergoing ECMO to treat seizures (18-20%) and withdrawal symptoms, with midazolam as a commonly used second-line drug to treat seizures or to sedate the newborn.[35] The distribution of phenobarbital, a lipophilic drug, was not affected by ECMO as the sodium salt formulation has good water solubility (logP= 1.77). In contrast, it was shown in two studies that the distribution of midazolam increased. Pokorná et al.[35] found similar high inter-individual PK variability for Vd and Cl and no statistical differences in Vd or Cl. The authors assumed that the physicochemical characteristics of phenobarbital resulted in differences in the distribution in comparison with ECMO-induced changes for typical lipophilic drugs. Michaličková et al.[34] found that the phenobarbital Cl increased in the time interval (day 1-12) studied within 12 days. Different loading and maintenance doses were used in both studies, and different Vd and Cl values were calculated. Because of the substantial unexplained variability, individual patients should consider regular and recurrent therapeutic drug monitoring and therapeutic concentration intervention, even with the model-derived regimen.[34]

Body weight was the main PK covariate of phenobarbital disposition.[35] In the study by Michaličková et al., the Vd of phenobarbital was not much affected by ECMO, while its Cl increased over time, especially in the first 12 days.[34] Both (body weight and postnatal age) rather reflect maturational covariates. Furthermore, there was still high unexplained variability.[34] In both studies, the suggested target range for phenobarbital therapeutic concentration was 10-40 mg/L.

Thibault et al.[36] created a popPK model for IV phenobarbital in neonates following cardiac surgery and ran simulations to find the optimal dose regimes. Loading doses of 30 and 20 mg/kg reached target concentration with albumin levels less than or equal to 3 and 3.5 mg/dL, respectively, in neonates not on ECMO. Also, loading doses of 30 mg/kg were effective on ECMO independent of albumin levels. In addition, all neonates attained target concentrations with maintenance doses of 4-5 mg/kg/d. The purpose of this study was to assess the effect of changed protein binding or, more likely, positive fluid balance in phenobarbital dosing (Table 11).

Theophylline

According to the Mulla et al.[37] study that determined popPK for theophylline during ECMO from routine monitoring data, the estimated Cl is significantly lower, and Vd higher, than previously reported in non-ECMO patients of similar age. These variations are most likely due to the increased circulation volume during ECMO as well as decreased renal and hepatic function in this population. The high inter-individual variability reflects the varied character of ECMO patients (Table 12).

DISCUSSION

Most of the studies included in the review were on antimicrobials including vancomycin, meropenem, fluconazole, gentamicin, cefotaxim, and cefepim. This confirm the pattern on drug utilization described by Buck et al in 2003[9] both drugs are hydrophilic, have a rather low Vd (L/kg) and a narrow therapeutic range. Vd relates the amount of drug in the body to the plasma concentration of the drugs, depending on the fluid in which concentration is measured.[38] Vd depends on substance characteristics and patient factors which can be different between neonates and adults.

In this literature review, because drug clearance is difficult to predict because of dynamic ontogenetic changes in renal function, ECMO received neonates and infants without concomitantly CRRT included to avoid heterogeneity.[39] Therefore, target concentration intervention based on serum concentrations is indispensable to ensure therapeutic exposure in this population.

Most studies found that patients undergoing ECMO had higher Vd and lower Cl than non-ECMO patients. The PK differences in which we have the highest confidence are from trials that included non-ECMO comparison groups. However, the bulk of the studies, did not include non-ECMO comparator groups, and the comparisons were based on PK data provided in other published data.[40] The differences in Vd and Cl of some of the studied drugs, such as vancomycin, between ECMO and non-ECMO controls demonstrated significant intra-study variability, with some studies showing increased values for the PK parameters[31 32 36], while others showed decreased values or no change.[23 24 41]

In this literature review, most studies evaluated both VV and VA modalities of ECMO together. According to the Bhatt-Mehta et al.[42] study, there was no statistically significant between VA and VV bypass type in terms of Vd (0.61 ± 0.15 vs. 0.74 ± 0.23 L/kg), Cl (0.157 ± 0.046 vs. 0.199 ± 0.085 L/h), and $t_{1/2}$ (10.04 ± 2.45 vs. 10.75 ± 3.43 h) (p>0.05).[42] Therefore, it is estimated that none of the included studies analyzed the VV-VA difference in terms of PK parameters.

In general, changes in tissue distribution caused by a severe illness are more likely to be clinically important for hydrophilic drugs that lack meaningful intracellular penetration and so have a low Vd.[43] Also, because neonates have a larger proportion of body water, the Vd per kg for water-soluble substances may be higher.[44] In addition to all these factors, it is reasonable to expect that the Vd of hydrophilic drugs will increase once the ECMO circulation is connected. This can be attributed to the circuit itself, as well as to the additional capillary leak commonly observed in these patients. To further illustrate this, all studies examining vancomycin and gentamicin consistently showed an increased Vd in neonates undergoing ECMO.[8 9]

Mulla et al.[30] have analyzed the PK of midazolam in neonates undergoing ECMO. Their midazolam model reveals a significantly altered Vd in ECMO patients, with a significant prolongation of the $t_{1/2}$ (from 6.8 to 33.3 hours). Mulla et al.[30] did not report a correlation between Cl and duration of infusion or PNA. They also determined the MR, a surrogate measure of CYP3A activity, as being higher than previous reports in (pre)term neonates and attribute this to a reduced renal elimination Cl of the metabolite. Similarly, in the study of Ahsman et al.[31], it was shown that the Vd increased. But unlike Mulla et al.[30], they stated that Cl increased 3-fold within the first 5 days. It is estimated that this is due to the difference in

the ECMO circuit construction (oxygenator). Ahsman et al.[31] also reported that concomitant inotropic infusion increased hydroxy-midazolam glucuronide Cl by 23% and midazolam dose could be increased starting from the 5th day.

Critical illness may significantly affect dexmedetomidine PK, mainly through decreased hepatic metabolism and elevated Vd induced by organ failure and inflammation, which may be modified further by the presence of ECMO. Increases in Cl result in higher dexmedetomidine concentrations, while increases in Vd result in lower concentrations. According to the Thibault et al.,[45] Exploration of PK data using previously published models resulted in overprediction of observed values, which might have theoretically suggested higher Vd and Cl. Adding a component on Vd, on the other hand, did not enhance their goodness of fit plots, implying that increasing Vd does not explain their findings. This study found that popPK models that are relevant to a wide range of ages and diseases are more feasible in paediatric critical care settings but more difficult to design.

Peters et al.[33] found that morphine Cl on ECMO lags behind that in healthy postoperative neonates of the same age but matures rapidly and was similar to the cohort of postoperative surgical neonates within two weeks. After this study, on the contrary, the same authors found that formation Cl to M3G is reduced during the first ten days of ECMO with the same study population.[17]

As a final reflection, we wanted to mention that we could not retrieve reports on any subsequent validation study for the adapted dosing regimens suggested. Furthermore, the reporting on toxicity and safety in these population PK studies is not present in these papers, so that additional studies to validate the adapted dosing regimens on efficacy and toxicity are warranted.[41] From a methodological perspective, better descriptions on the pathophysiology over time can be very useful to feed (patho)physiology-based PK models as illustrated for fluconazole PK over the human age span, including neonates.[8 46] Previously, Hoie et al.[47] had recommended a vancomycin dose of 20 mg/kg at an 18-h interval for infants on ECMO with serum creatinine levels of <1.5 mg/dl. However, Amaker et al.[41] data indicate that infants on ECMO with serum creatinine levels of <1.5 mg/dl should be given vancomycin no more frequently than every 24 h. In comparison with previously published data, the neonates

undergoing ECMO in this study demonstrated a much larger Vd, a lower Cl, and a longer $t_{1/2}$ with an individual PK study.

This paper has its strengths and limitations. The predefined approach to focus on population PK studies has limitations, but these methods does provide the best approach to analysis trends over time, as well as covariates involved. Furthermore, the search strategy was structured, but not compliant with all guidelines (like number of databases searched) relevant for a meta-analysis.

CONCLUSION

The aim of this paper was to determine the effect of ECMO use on PK in neonates, based on a systematic assessment of population PK studies. At present, there are a limited number of population PK studies for a limited number of compounds reported in neonates undergoing ECMO. Despite some differences in results for the same drug, the general pattern suggests an increase in Vd and $t_{1/2}$, a stable to decreased Cl, and an increase in intra- and interpatient variability on ECMO. There was no any relevant toxicity and safety parameters reported, including in those studies with more than 100% increased PK parameters. Therefore, we recommend more studies are needed to address this toxicity and safety concern. Consequently, and if possible, therapeutic drug monitoring and target concentration intervention are strongly recommended to determine the appropriate exposure and doses for neonates undergoing ECMO.

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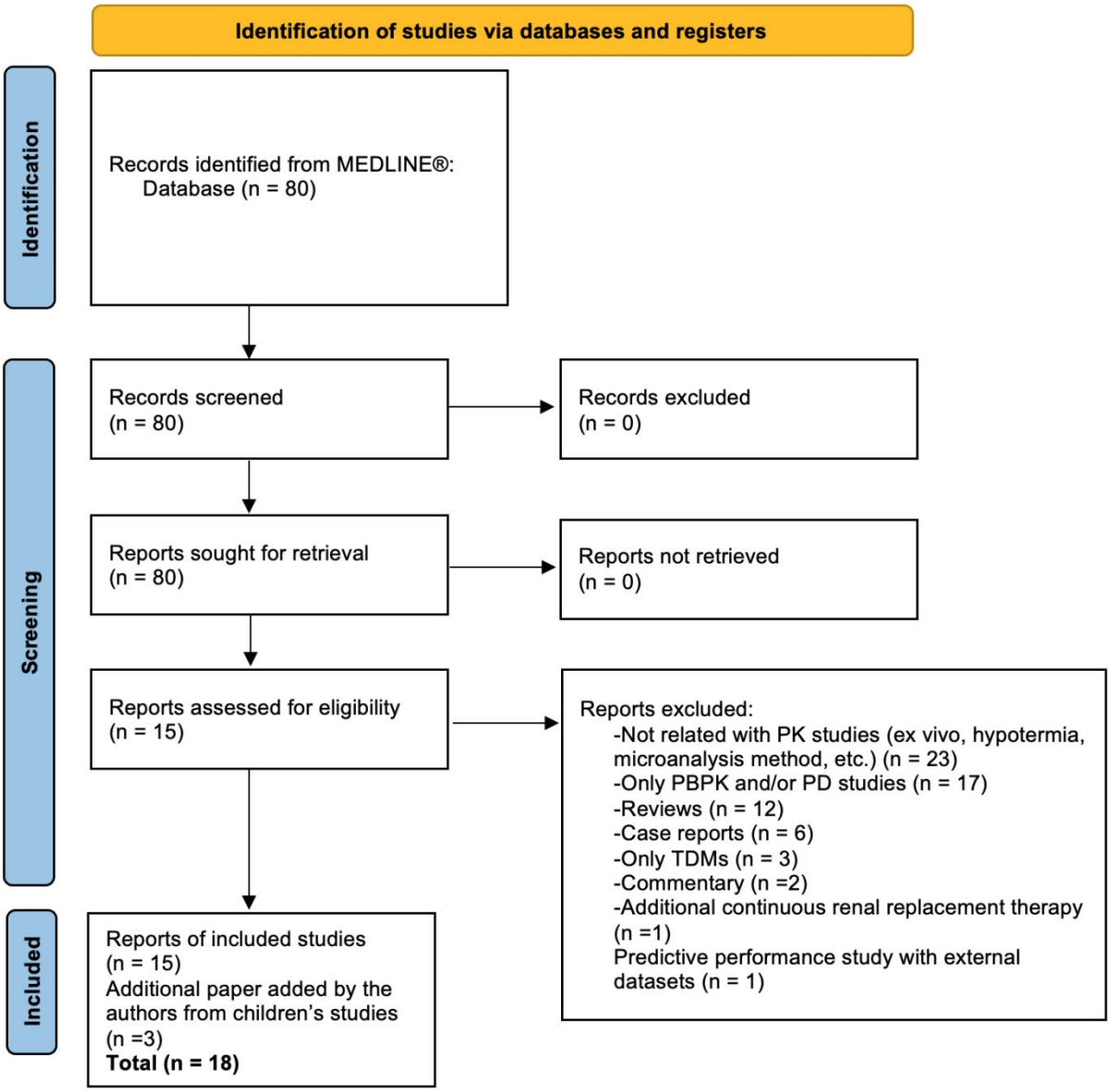
Figure 1. PRISMA flow diagram of data selection and subsequent results



MEDLINE: Medical Literature Analysis and Retrieval System Online, PK: Pharmacokinetics, PBPK: Physiologically based pharmacokinetic modelling, PD: Pharmacodynamics, TDM: Therapeutic drug monitoring

Table 1. Study characteristics (N=18)

Characteristics	**n**
Type of Study	
Prospective observational	11
Retrospective observational	6
Prospective & Retrospective	1
Drug	
Vancomycin	4
Meropenem	2
Fluconazol	1
Gentamicin	2
Cefepime	2
Midazolam	2
Phenobarbital	2
Theophylline	1
Clonidine	1
Morphine	1
Cefotaxime	1
ECMO Modality	
Veno-venous	-
Veno-arterial	2
Mixed	16
Pharmacokinetic Parameters	
Absorption	-
Distribution	16
Metabolic clearance	2
Renal clearence	17

Table 2. Characteristics of the studies, pharmacokinetics, and dose recommendations related to vancomycin

Study	n	PNA	Weight	Type	Group	Model	Modality	Administered Dose	V_d	C_L	$t_{1/2}$ (hours)	Recommended Dose
*Mulla et al[21] 2005, UK**	15	8.2	3.5	P&R	children	2-comp with WinNonMix	VV-VA	10–15mg/kg q6-24h	0.45 ± 0.1 L/kg	0.04± 0.02 L/kg/h	10.40 ±6.67	-
*Cies et al[18] et al 2017, USA***	12	9.5	3.1	R	neonates	1-comp with Pmetrics	VV-VA	10–15mg/kg q8-24h	1.2 ± 0.4 L/kg	0.21 ± 0.08 L/kg/h	14.1 ± 6.9	-
*Zylbersztajn et al[19] 2021, Chile****		24 (2-132) months	10 (3.5-37)	P	children	2-comp with PMetrics	VV-VA	10-15 mg/kg q6-12h	0.42 ± 0.28 L/kg	0.06 ± 0.05 L/kg/h	-	Across each dosing interval 63.6% of patients achieved the PK/PD targets for adequate exposure.
*Moffett et al[20] 2018, USA****	N: 28 I: 28	0.64 (0.07-6.7) years	7.6 (3.7-21.9)	R	children	2-comp with NONMEM	VV-VA	25 mg/kg q18h for neonates 30 mg/kg q12h for infants	$Vd_{central}$: 0.36 L/kg $Vd_{peripheral}$: 0.46 L/kg -	0.06 L/kg/h -	-	25–30 mg/kg/dose q12–24 h with serum concentration monitoring is a reasonable empiric dosing strategy to obtain an area under the curve for 24 h greater than 400.

N: Neonates, I: Infants, VV: Veno-venous, VA: veno-arterial, R: Retrospective, P: Prospective, LD: Loading dose, MD: Maintenance dose, CI: Continuous infusion
Boldface fonts represent comparisons to controls within the same study. In other studies, they represent comparisons to non-ECMO neonates from a different published study.
* The reference range for serum vancomycin concentrations was trough 5-15 mg/L.
** The reference range for serum vancomycin concentrations was trough >10 mg/L.
*** The reference range for serum vancomycin concentrations was trough <15 mg/L.

Table 3. Characteristics of the studies, pharmacokinetics, and dose recommendations related to meropenem

Study	n	PNA	Weight	Type	Group	Model	Modality	Administered Dose	V_d	C_L	$t_{1/2}$ (hours)	Recommended Dose
Wang et al[23] 2021, China	9*	2.00 (0.71-3.88) years	11.50 (9.50-36.30)	P	children	2-comp with first order Elimination with NONMEM	VV-VA	20-40 mg/kg q8h	-	11.59 (5.92–20.19) vs 13.51 (3.71-20.80) L/h **↓14.2% (compared to controls)** 11.59 (5.92–20.19) vs 7.9 ± 5.9 L/h ↑46.7% (compared to adults)	-	The authors recommended the opitimized dosing regimens for septic children receiving ECMO depending on the PTA of PK target 50%T > MIC and 100%T > MIC, for children with sepsis during ECMO with different body weight, estimated Cl and MIC of bacteria.
Zylbersztajn et al.[19] 2021, Chile	9	48 (2–165) months	16 (3.5–45)	P	children	2-comp with PMetrics	VV-VA	20-40 mg/kg q8-12h	0.289 ± 0.295 L/kg -	0.139 ± 0.102 L/h/kg -	-	Across each dosing interval 91% of patients achieved the PK/PD targets for adequate exposure for meropenem. Higher dosing with extended infusion were needed in the meropenem administration.

VV: Veno-venous, VA: veno-arterial, R: Retrospective, P: Prospective, LD: Loading dose, MD: Maintenance dose, CI: Continuous infusion, PTA: probability of target attainment, MIC: minimum inhibitor concentration
Boldface fonts represent comparisons to controls within the same study. In other studies, they represent comparisons to non-ECMO neonates from a different published study.
*Number of patients undergoing only ECMO circuit.

Table 4. Characteristics of the studies, pharmacokinetics, and dose recommendations of isolated studies on fluconazole

Study	n	PNA	Weight	Study design	Group	Model	Modality	Administered Dose	V_d	Cl	$t_{1/2}$ (hours)	Recommended Dose
Watt et al[24] 2015, USA	40	22	3.4	P 2-groups	infants	1-comp. with NONMEM	VV	25 mg/kg loading dose followed 12 mg/kg/day maintenance therapy	For neonates (ECMO vs. non-ECMO): 1.5 (1.3, 1.8) vs. 0.96 (0.55, 1.4) L/kg **↑56.2%** For infants (ECMO vs. non-ECMO): 1.2 (0.91, 1.6) vs. 0.83 (0.72, 1.0) L/kg **↑44.6%**	For neonates (ECMO vs. non-ECMO): 0.018 (0.013, 0.04[illegible] vs. 0.018 (0.008, 0.04[illegible] L/h/kg **↔** For infants (ECMO vs. non-ECMO): 0.022 (0.011, 0.03[illegible] 0.017 (0.008, 0.02[illegible] L/h/kg **↑29.4%**	-	12 mg/kg for prophylaxis 35 mg/kg for invasive candidiasis treatment

VV: Veno-venous, VA: veno-arterial, R: Retrospective, P: Prospective, NONMEM: Nonlinear mixed-effects modelling, LD: Loading dose, MD: Maintenance dose, CI: Continuous infusion6
Boldface fonts represent comparisons to controls within the same study. In other studies, they represent comparisons to non-ECMO neonates from a different published study

Table 5. Characteristics of the studies, pharmacokinetics, and dose recommendations related to gentamicin

Study	n	PNA	Weight	Study design	Group	Model	Modality	Administered Dose	V_d	Cl	$t_{1/2}$ (hours)	Recommended Dose
Dodge et al 1994, USA[25]	11	37-42 PMA	2.67-5.10	P 1-group	Neonates and infants	1-comp with NPEM	VV-VA	2.5 mg/kg loading dose and q8-12h maintenance dose	From 0.748 L/kg to 0.471 L/kg after ECMO was discontinued **↑58.8%**	From 0.239 L/h to 0.350 L/h after ECMO was discontinued **↓31.7%**	From 9.24 h to 3.87 h after ECMO was discontinued **↑138.7%**	4.3 mg/kg loading dose 3.7 mg/kg q18-24h maintenance dose
Moffett et al 2018, USA[22]	N: 28 I:5	0.17 (0.12 - 0.82) m	3.1 (2.4-3.8)	R 1-group	Mostly neonates and infants	2-comp with NONMEM	VV-VA	1.8 mg/kg/dose	0.60 L/kg -	0.03 L/kg/h -	-	Children with elevated serum creatinine values should have extended dosing intervals (4-5 mg(kg/day).

N: Neonates, I: Infants, VV: Veno-venous, VA: veno-arterial, R: Retrospective, P: Prospective, NPEM: Nonparametric expectation and maximization, LD: Loading dose, MD: Maintenance dose, CI: Continuous infusion
Boldface fonts represent comparisons to controls within the same study. In other studies, they represent comparisons to non-ECMO neonates from a different published study.

Table 6. Characteristics of the studies, pharmacokinetics, and dose recommendations of isolated studies on cefotaxime

Study	n	PNA	Weight	Study design	Group	Model	Modality	Administered Dose	V_d	C_L	$t_{1/2}$ (hours)	Recommended Dose
Ahsman et al[26] 2010, the Netherlands	37	3.3 (0.67-199)	3.5 (2.0-6.2)	P 1-group	neonates	1-comp. with NONMEM	VV-VA	50 mg/kg q12h (PNA<1 w) 50 mg/kg q8h (1<PNA<4 w) 37.5 mg/kg q6h (PNA>4 w)	ECMO vs. non-ECMO: 1.82 L vs. 0.68 to 1.14 L **↑59.6-167.6%**	ECMO vs. non-ECMO: 0.36 L/h vs. 0.20 to 0.55 L/h ↔	3.5 h	The standard cefotaxime dose regimen provides a sufficiently high $t_{>MIC}$ in infants undergoing ECMO.

IQR: Interquartile range, VV: Veno-venous, VA: veno-arterial, R: Retrospective, P: Prospective, NONMEM: Nonlinear mixed-effects modelling, LD: Loading dose, MD: Maintenance dose, CI: Continuous infusion, MIC: Minimum inhibitor concentration

Boldface fonts represent comparisons to controls within the same study. In other studies, they represent comparisons to non-ECMO neonates from a different published study

Table 7. Characteristics of the studies, pharmacokinetics, and dose recommendations of isolated studies on cefepime

Study	n	PNA	Weight	Study design	Group	Model	Modality	Administered Dose	V_d	CL	$t_{1/2}$ (hours)	Recommended Dose
Thibault et al[27] *2022, USA*	9/17	0.5 (0.2-2.5) m	4.4 (3.5-4.6)	P 1-group	Children	2-comp. with NONMEM	VV-VA	50 mg/kg q6-24h or 100-150 mg/kg/d continuous infusion	Vc + Vp = 0.6 L/kg	410 ml/h/4.4 kg	-	Dosing regimens of 50mg/kg q8h reached optimal concentrations at an MIC of 8mg/L based on simulations.
Zuppa et al[28] *2019, USA*	17	1.3-22 m	3.3-10	P 1-group	infants	2-comp with NONMEM	VV-VA	50 mg/kg q8-24h	Vc + Vp = 0.4 L/kg **↑250%**	7.1mL/min/3.8 kg **↓26.6%**	-	For free cefepime, only 14 of the 19 doses (74%) demonstrated a *fT*_MIC of 16 mg/L, an appropriate target for the treatment of *pseudomonal* infections, for greater than 70% of the dosing interval.

IQR: Interquartile range, VV: Veno-venous, VA: veno-arterial, R: Retrospective, P: Prospective, NONMEM: Nonlinear mixed-effects modelling, LD: Loading dose, MD: Maintenance dose, CI: Continuous infusion, MIC: Minimum inhibitor concentration

Boldface fonts represent comparisons to controls within the same study. In other studies, they represent comparisons to non-ECMO neonates from a different published study

Table 8. Characteristics of the studies, pharmacokinetics, and dose recommendations related to midazolam

Study	n	PNA	Weight	Study design	Group	Model	Modality	Administered Dose	V_d	C_L	$t_{1/2}$ (hours)	Recommended Dose
Mulla et al 2003, UK[30]	19	3.8	3.4	P Random 2-groups	neonates	1-comp. with WinNonMix	VV-VA	50-250 µg /kg/h	From 0.8±0.5 to 4.1±0.5 L/kg **↑412.5%**	1.4 ± 015 mL/kg -	From 6.8 (2.2–39.8) to 33.3 (7.4-178) **↑389.7%**	LD: 350 µg /kg/h for 6 hours MD: 50 µg /kg/h
Ahsman et al[31] *et al 2010, the Netherlands*	20	0.79	3.0	P 1-group	neonates	A two-compartment model for midazolam and a one-compartment model for the metabolites with NONMEM	VA	LD: 0.2 mg/kg bolus MD: 0.1 mg/kg/h CI	Midazolam: 14.6 L/3kg 1-hydroxymidazolam: 10.2 L/3 kg Hydroxymidazolam glucuronide: 1.21 L/3 kg **↑240.3%**	Midazolam: 1.38 L/h/3 kg 1-hydroxymidazolam: 1.03 L/h/3 kg Hydroxymidazolam glucuronide: 0.18 L/h/3 kg **↑300.0%**	1.85 -	LD: 300 µg /kg/h for 6 hours MD: 150 µg /kg/h

VV: Veno-venous, VA: veno-arterial, R: Retrospective, P: Prospective, NONMEM: Nonlinear mixed-effects modelling, LD: Loading dose, MD: Maintenance dose, CI: Continuous infusion
Boldface fonts represent comparisons to controls within the same study. In other studies, they represent comparisons to non-ECMO neonates from a different published study.

Table 9. Characteristics of the studies, pharmacokinetics, and dose recommendations of isolated studies on clonidine

Study	n	PNA	Weight	Study design	Group	Model	Modality	Administered Dose	V_d	C_L	$t_{1/2}$ (hours)	Recommended Dose
Kleiber et al[32] 2017, the Netherlands	22	1 (IQR 6.4) m	4 (IQR 3.1)	P 2-groups	Children	1-comp. with NONMEM	VV-VA	0.24 (0.15) µg/kg/h infusion	454 L/70 kg at ECMO start **↑55%**	29.9 L/h/70 kg at ECMO start **↑200%**	-	The authors simulated the number of bolus doses of 5 µg/kg needed to reach the target concentration of 2 ng/ml within 1 h: three repeated bolus doses of 5 µg/kg were needed.

IQR: Interquartile range, VV: Veno-venous, VA: veno-arterial, R: Retrospective, P: Prospective, NONMEM: Nonlinear mixed-effects modelling, LD: Loading dose, MD: Maintenance dose, CI: Continuous infusion6
Boldface fonts represent comparisons to controls within the same study. In other studies, they represent comparisons to non-ECMO neonates from a different published study

Table 10. Characteristics of the studies, pharmacokinetics, and dose recommendations of isolated studies on morphine

Study	n	PNA	Weight	Study design	Group	Model	Modality	Administered Dose	V_d	Cl	$t_{1/2}$ (hours)	Recommended Dose
Peters et al[33] 2005, the Netherlands	14	82	4.2	P	infants	1-comp. with NONMEM	VA	LD: 100 µg /kg MD: 40 µg /kg/h	Day 1: 1.89 mL/kg/min Day 10: 3.33 mL/kg/min **↑76.2%**	Day 1: 1.1 mL/kg/min Day 10: 6.0 mL/kg/min **↑445.5%**	-	Serum concentrations decrease during the first 10 days of ECMO, and that dose adjustments should be carried out.

VV: Veno-venous, VA: veno-arterial, R: Retrospective, P: Prospective, LD: Loading dose, MD: Maintenance dose, CI: Continuous infusion6
Boldface fonts represent comparisons to controls within the same study. In other studies, they represent comparisons to non-ECMO neonates from a different published study

Table 11. Characteristics of the studies, pharmacokinetics, and dose recommendations related to phenobarbital

Study	n	PNA	Weight	Type	Group	Model	Modality	Administered Dose	V_d	C_L	$t_{1/2}$ (hours)	Recommended Dose
Michaličková et al[34] et al 2020, Czech Republic	13	2	3.21	R	neonates	1-comp with NONMEM	VV-VA	LD: 7.5mg/kg (8.5–16mg/kg) MD: 6.9mg/kg/d (4.5–8.5 mg/kg/d).	2.72 L	0.0096 L/h	-	In the first 12 days of ECMO with a regimen of a LD of 20 mg/kg and a MD of 4 mg/kg/d divided in two doses with an increase of 0.25 mg/kg every 12 hours during ECMO
Thibault et al[36] 2020, USA	12/37*	5 (0-26)	3.2 (1.3-3.8)	R	neonates	1-comp with first-order elimination with NONMEM	VV-VA	LD: 15-20 mg/kg MD: 3-6 mg/kg/d	**↑22%** (Normalization of albumin values from 2.5 mg/dL to 3.5 mg/dL decreased the estimated V by 13%)	**↑114%** (Over the first 20 days of life)	-	LD 30 mg/kg achieved goal peak concentration. MD of 4-5 mg/kg/d sustained goal trough concentration

VV: Veno-venous, VA: veno-arterial, R: Retrospective, P: Prospective, LD: Loading dose, MD: Maintenance dose, CI: Continuous infusion
Boldface fonts represent comparisons to controls within the same study. In other studies, they represent comparisons to non-ECMO neonates from a different published study.
*Number of patients undergoing only ECMO circuit.

Table 12. Characteristics of the studies, pharmacokinetics, and dose recommendations related to theophylline

Study	n	PNA	Weight	Study design	Group	Model	Modality	Administered Dose	V_d	C_L	$t_{1/2}$ (hours)	Recommended Dose
Mulla et al[37] 2003, UK	N: 38 I: 14	8.4 ± 5.9 for neonates 122 ± 107 for infants	3.3 ± 0.5 for neonates 4.8 ± 2.0 for infants	R 1-group compared with the literature	Children	1-comp. with first order elimination with Win-NonMix Professional	VV-VA	9.2 ± 2.6 µg/kg/min infusion	The interindividual variability **↑40%**	The interindividual variability **↓38%**	-	Maintenance infusion rates following an initial loading dose (0.57 x weight (kg) x 10 mg/L). Maintenance infusion rate calculated from: average steady-state concentration = rate of infusion/clearance (using clearance parameters determined in the final model).

N: Neonates, I: Infants, VV: Veno-venous, VA: veno-arterial, R: Retrospective, P: Prospective, NONMEM: Nonlinear mixed-effects modelling, LD: Loading dose, MD: Maintenance dose, CI: Continuous infusion6
Boldface fonts represent comparisons to controls within the same study. In other studies, they represent comparisons to non-ECMO neonates from a different published study

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Population Pharmacokinetics in Critically Ill Neonates and Infants Undergoing Extracorporeal Membrane Oxygenation: A Literature Review

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Abstract

Extracorporeal membrane oxygenation (ECMO) increases circulating blood volume, capillary leak, and temporarily alters kidney function. Consequently, pharmacokinetics (PK) can be affected. When applied to neonates and infants, additional dose adjustments are a major concern, as the volume of distribution (Vd) is already generally greater for water-soluble drugs and the clearance (Cl) of drugs eliminated by glomerular filtration is reduced. A systematic search was performed on MEDLINE® (1994-2022) using a combination of the following search terms: "pharmacokinetics", "extracorporeal membrane oxygenation", and "infant, newborn" using MeSH search strategy. Nine out of 18 studies on 11 different drugs (vancomycin, meropenem, fluconazole, gentamicin, midazolam, phenobarbital, theophylline, clonidine, morphine, cefotaxime, and cefepime) recommended dose increase/decrease by determining PK parameters. In other studies, it has been suggested to adjust the dose intervals. While the $t_{1/2}$ and Vd mostly increased for all drugs, the Cl of the drugs has been shown to be variability except for midazolam and morphine. There are a limited number of population PK studies in neonates and infants undergoing ECMO circuits. Despite some divergences, the general pattern suggests an increase in Vd and $t_{1/2}$, an increased, stable or decreased Cl, and an increase in variability. Consequently, and if possible, therapeutic drug monitoring and target concentration intervention are strongly recommended to determine appropriate exposure and doses for neonates and infants undergoing ECMO support.

Keywords: neonates; infants; pharmacokinetics; ECMO; antimicrobials; anticonvulsants; sedo-analgesics

Key messages

- An increase in volume of distrubition (Vd) of many drugs in ECMO cohorts is observed.
- Variable effects on clearance due to ECMO.
- Therapeutic drug monitoring and target concentration intervention are strongly recommended to determine appropriate exposure and doses for neonates and infants undergoing ECMO.
- There have been very few studies of the effect of ECMO on population PK data in neonates and infants.
- We identified on 11 drugs (vancomycin, meropenem, fluconazol, gentamicin, midazolam, phenobarbital, theophylline, clonidine, morphine, cefotaxime, and cefepime).

INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) is a cardiopulmonary bypass procedure used to provide temporary respiratory or cardiac support to critically ill patients, including neonates and infants.[1 2] ECMO has two cannulation techniques: veno-venous (VV) and veno-arterial (VA). Veno-venous ECMO is mainly used for patients with respiratory failure, while veno-arterial ECMO support is rather used in patients with cardiac failure.[3 4]

While polypharmacy is well recognized in hospitalized adults, it is also quite common in hospitalized neonates and infants in intensive care units (ICU). Because survival and overall outcome rely on medicines, effective drug therapy is essential to improve care and minimize adverse effects.[5 6] This includes targeted dosing and exposure, but necessitates understanding and data on pharmacokinetic (PK) changes related to ECMO use in this specific population of neonates.

Volume of distribution (Vd), which specifies the dosage necessary to generate the desired peak concentration, and clearance (Cl), which is the volume of fluid cleared of drug from the body per unit of time, are the fundamental drivers of drug pharmacokinetics (PK). Vd and Cl are also important drivers of elimination half-life ($t_{1/2}$). The $t_{1/2}$ can be calculated with the following simple formula:

- $t_{1/2} = 0.693 * Vd/Cl$

Although an approximate, from a clinical point of view, this formula relates $t_{½}$ to Vd, CL, and steady-state, which represent the basic PK parameters.[7]

Understanding the parameters impacting medication PK and PD in the complicated setting of patient immaturity, severe illness, (multi)organ failure, and the necessity for supportive extracorporeal circuits is crucial for safe and successful prescription in neonates and infants undergoing ECMO.[8] Many medications' PK can be impacted by ECMO since it raises circulating blood volume, causes capillary leak, and temporarily affects renal function.

The underlying mechanisms related to the additional (non)-maturational changes in PK during ECMO are diverse, and in part related to the ECMO equipment, the impact of the technique, and the medical condition of the neonates and infants.[9] The ECMO equipment alters drug

exposure through adsorption by circuit components. This is to a certain extent drug-specific, and is more pronounced for drugs with high lipophylicity.[10] The need for ECMO will results in shift in fluid balance, capillary leak, and also in renal impairment; Acute kidney injury (AKI) is common in ECMO or cardiac bypass cases.[8 11 12] Finally, the medical condition like sepsis, or cardiac failure in itself will affect PK.[13] These non-maturational factors add on to the maturational PK of many drugs in neonates, different from those in adults.

All of these PK parameters (absorption, distribution, metabolism, and elimination, or ADME) exhibit maturation (age or weight-dependent alterations), but they are also influenced by non-maturational variables (disease, treatment, co-medications, environment or genetic background).[13] The Vd in neonates is usually larger for water-soluble drugs. Therefore, the Vd is generally increased, whereas Cl is decreased in neonates undergoing ECMO, especially for drugs cleared by renal route.[10-12] There are some variations in the Vd due to body composition, blood flow, protein binding, and membrane permeability.[14] Because renal clearance of metabolites is decreased in preterm and term infants, active metabolites may accumulate.[15]

According to the current literature, we aware that many pharmacological treatments in neonates and infants undergoing ECMO have not been fully studied and the risk-benefit ratios are not clearly defined. The aim of this literature review is therefore to provide an overview of the effects of ECMO on drug PK parameters in neonates (postnatal age 0-28 days) and infants (birth to 1-year old), specifically clearance, Vd, $t_{1/2}$ with recommended doses.

METHODS

A systematic literature search was performed on MEDLINE® (National Library of Medicine PubMed) of all literature between January 1994 and February 2022 in the PubMed database in September 2022. The search was made using of following keywords "pharmacokinetics", "extracorporeal membrane oxygenation", "infant, newborn". In MEDLINE® the corresponding MeSH search strategy for these search terms as the main heading (descriptor) were used.[16] 'AND' was used to separate the main search terms. Papers meeting the following criteria were accepted for the study:

- Full-text written in English,
- Concerned the human species,

- Research articles (clinical study, comparative study, multicenter study, observational study etc.),
- The reporting of a PK parameter for at least one of the absorption, distribution, metabolism, or excretion (ADME) process,
- Full-text is available,
- The references and citations of the retained papers were checked (backward snowball method),
- If necessary, additional paper added by the authors.

Articles were excluded if the study population did not include neonates/infants, or if only ECMO (like e.g., concomitant continuous renal replacement therapy (CRTT)) was not applied. Also, case reports, case series, reviews, commentaries, and guidelines were excluded, as we only focused on population pharmacokinetic studies. Physiologically based pharmacokinetics and TDM studies were excluded. Full-texts for all papers were retrieved through various research databases.

First, the titles of all articles were screened. If the relevance was unsure, the abstract was subsequently read. Finally, the resulting selected articles were thoroughly studied, and the references were screened for secondary inclusion after both authors (NS and NY) reach a consensus. All references and citations to the included articles verificated, and no additional studies were identified to be included. Furthermore, an additional search was performed by the authors using the keywords "pharmacokinetics", "extracorporeal membrane oxygenation" and "paediatrics" from MeSH search terms to identify studies with the paediatric population that included newborn and/or infant patients undergoing ECMO circuit.

Patient and public involvement

This study was done without the participation of patients or parents. Patients or parents were not invited to comment on the trial design, nor were they contacted to define patient-relevant outcomes or interpret the findings. Patients or parents were not asked to help write or revise this text for readability or accuracy.

RESULTS

In this search, in total 16 papers were retained with the keyword's "pharmacokinetics", "extracorporeal membrane oxygenation", "infant, newborn". One article related morphine metabolite was excluded because it was a follow-up to another article with the same study protocol and population.[17] There are also 3 additional papers from 135 results added by the authors from children's studies including newborns and/or infants' data. In this manner, the literature review was completed with a total of 18 papers. The articles were published in the MEDLINE® database starting in 1994 (1 report before 2000, 4 between 2000-2009, 7 between 2010-2019, and already 6 reports from 2020 onwards), with a variety of nations participating (depending on the corresponding author). There were no additional articles were found matching the inclusion criteria with the backward snowball method. A flow diagram of data selection, reasons for exclusion, and subsequent results are provided in Figure 1.

Characteristics of included studies (n=18) are provided in Table 1. One of the included studies was both prospective and retrospective. Most of the drugs studied are antibiotics (vancomycin, meropenem, fluconazole, and gentamicin), followed by midazolam and phenobarbital. The route of administration was intravenous in all studies. Therefore, enteral absorption was not evaluated. Studies were limited to the mother compounds, except for data on the PK parameters of midazolam and morphine metabolites. Vd and Cl parameters were reported in all studies. The clinical characteristics reflect the population of interest (late preterm, term neonates, and infants), with a diversity of pathologies, but without sufficient details to further explore this.

Antimicrobials

Vancomycin

Similar results were observed for vancomycin Cl, while findings on Vd were consistent between the 4 studies retrieved (Table 2). In all of these studies, it was observed that while Cl decreased, Vd increased for the patients undergoing ECMO circuits. In the study of Cies et al.[18], the vancomycin Cl increased in the presence of ECMO, so that it was suggested to use a higher dose in these patients. The authors attributed this increased Cl to the specific ECMO circuit used. In all of these studies, the target range for vancomycin trough concentration was

determined as greater than 10 mg/L[18], less than 15 mg/L[19 20] or 5-15 mg/L[21]. In addition, in these 4 articles, the Vd of vancomycin increased in the presence of ECMO, be it not statistically significant in the individual studies.

In the Zylbersztajn[19] et al study, the PK/PD target was a ratio of >400 of the area under the curve to the minimum inhibitory concentration (AUC/MIC). Weight was also included as a covariate on both central Vd and Cl, and serum creatinine was also included on Cl for vancomycin. Furthermore, four vancomycin PK profiles met the lower PK/PD target, three of which corresponded to a dose of 15 mg/kg every 6 h. 63.6% of patients met the therapeutic achievement for sufficient exposure across all dosage intervals.

Moffett et al.[22] described the PK of vancomycin in paediatric patients undergoing ECMO and provide dosing recommendations. Serum creatinine level and postmenstrual age were significant factors for Cl, patient age for central Vd, and albumin for peripheral Vd in this investigation. Furthermore, the simulation indicated a dosage of 25-30 mg/kg/dose every 12-24 hours as having the largest percentage of individuals with an AUC for 24 hours larger than 400 and trough values less than 15 mg/L. Serum vancomycin concentration monitoring is recommended in paediatric patients undergoing ECMO circuits.

Meropenem

Two studies looked at meropenem (Table 3). Because of the low meropenem adsorption in the ECMO circuit and the high dialysate rate in CRRT, the effects of ECMO and CRRT vary. This is mostly due to meropenem's chemical characteristics. According to the Wang et al.[23] study about a popPK model of meropenem in children with sepsis receiving extracorporeal life support, The PK characteristics of meropenem were not affected by ECMO intervention. Furthermore, ECMO and CRRT can raise Vd due to the extracorporeal circuits, although this study indicated that the impact on meropenem concentration was smaller than previously documented hemofilters. In summary, there was no significant changes in PK parameters were observed in children with sepsis who were receiving ECMO. However, this study harbors some conspicuous limitations due to limited data and sample size. For this reason, we need more data on meropenem for children with sepsis undergoing ECMO circuit.

Zylbersztajn et al.[19] described primary PK/PD parameters of meropenem and vancomycin in paediatric patients undergoing ECMO. For meropenem, weight was added as a covariate on volume of the central compartment (Vc). To conclude, the authors suggested that maximal meropenem dose utilizing a prolonged infusion and at least current vancomycin dosing with therapeutic drug monitoring are required to achieve adequate PK/PD targets in this patient population (Table 3).

Fluconazole

The ECMO circuits can alter drug PK; therefore, standard fluconazole dosing may result in suboptimal drug exposures and efficacy. According to the Watt et al.[24] study, the fluconazole Vd was increased in neonates and infants supported by ECMO. Although the fluconazole Cl was not changed in neonates, it was increased in infants undergoing ECMO. As a result, children on ECMO who develop invasive candidiasis require a fluconazole loading dose of 35 mg/kg, followed by a daily maintenance dose of 12 mg/kg to achieve exposures comparable to those obtained in children who are not on ECMO and are loaded with 25 mg/kg and maintained on 12 mg/kg daily. However, children above the age of two are underrepresented in this study, and the findings should be generalized with caution to this demographic. As a result, confirmatory prospective clinical studies evaluating fluconazole exposure, safety, and effectiveness in this group are required (Table 4).

Gentamicin

Two articles examining the popPK of gentamicin in the presence of ECMO were reviewed. Dodge et al.[25] show that while undergoing ECMO, neonates have a higher Vd for gentamicin, a lower Cl, and a much longer $t_{1/2}$. Based on these findings, the required peak and trough plasma gentamicin concentrations for neonates receiving ECMO circuits (5-8 and 2 g/ml, respectively) were achieved. They recommended a loading dose of gentamicin (4.3 mg/kg) and a maintenance dose (3.7 mg/kg q18-24h) followed by monitoring of serum concentrations and appropriate dose adjustments thereafter. Moffett et al.[22] found that children had elevated trough concentrations when gentamicin dosed according to standard dosing procedures. Therefore, fat-free mass should be used to dose gentamicin in patients undergoing ECMO circuit. Serum creatinine is also a marker of gentamicin clearance and should be used to change gentamicin dose in paediatric patients (Table 5). In all of these

studies, the target range for gentamicin peak concentration was determined as approximately 6 mg/L.

Cefotaxime

Cefotaxime can be excreted unchanged or after hepatic conversion into its active metabolite via the renal system in adults. There may be an inverse correlation between renal function and elimination $t_{1/2}$, notably for desacetylcefotaxime as an active metabolite. According to the Ahsman et al.[26] study, the standard cefotaxime dosing regimen produces a high enough $t_{>MIC}$. The Vd was greater in ECMO patients than in non-ECMO patients (1.82 vs. 0.68 to 1.14 L), while cefotaxime Cl levels were similar. To effectively treat neonates undergoing ECMO, a dosage regimen of 50 mg/kg q12h (PNA, 1 week), 50 mg/kg q8h (PNA, 1 to 4 weeks), or 37.5 mg/kg q6h (PNA, >4 weeks) can be used (Table 6).

Cefepime

According to the current literature, the increase in peripheral Vd caused by blood transfusion is explained by the volume received than by the kind of fluids obtained. Also, cefepime is a hydrophilic drug with minimal protein binding, and fluid administration may improve its Vd. In the Thibault et al.[27] study, in paediatric patients undergoing ECMO, renal function was a key driver of cefepime Cl. Based on simulations, dosing regimens of 50mg/kg given every 8 hours resulted in optimum serum concentrations at a MIC of 8mg/L. Indeed, with lower MICs and greater serum creatinine levels, longer dose intervals were adequate (Table 7).

According to the Zuppa et al.[28] study, cefepime clearance was reduced compared with previously reported data in children not receiving ECMO.[29] Furthermore, the Vd of cefepime with the use of ECMO can increase about 2.5-fold compared with the volume without the use of ECMO, as a result, the total quantity of cefepime accessible for clearance is reduced. At the end of the study, it was concluded that only %74 doses revealed a *fT* MIC of 16 mg/L for more than 70% of the dosing interval. As a result, cefepime TDM should be evaluated in the clinical setting to improve the ability to achieve therapeutic targets while limiting possible toxicity.

Sedatives & Analgesics

Midazolam

Two articles reported on midazolam PK in patients undergoing ECMO. Mulla et al.[30] reported that both the Vd and $t_{1/2}$ of midazolam increased. Clearance was 1.4 (SD 0.15) ml/kg/min, so that simulations with conventional doses resulted in excess levels. Altered PK may reflect sequestration of midazolam by components of the ECMO circuit. Besides, Ahsman et al.[31] reported an increased Vd and $t_{1/2}$, as well as a 3-fold increase in midazolam and 1-hydroxy-midazolam Cl in the first 5 days following ECMO initiation. Interestingly, concomitant inotropic infusion during ECMO increased 1-hydroxy-midazolam glucuronide Cl by 23%. They also determined the 1-hydroxy-midazolam/midazolam metabolic ratio (MR), a surrogate measure of cytochrome P450(CYP)3A activity, as being higher than previous reports in (pre)term neonates and attribute the reduced renal elimination Cl of the metabolite (Table 8).

Mulla et al.[30] have analyzed the PK of midazolam in neonates undergoing ECMO. Their midazolam model reveals a significantly altered Vd in ECMO patients, with a significant prolongation of the $t_{1/2}$ (from 6.8 to 33.3 hours). Mulla et al.[30] did not report a correlation between Cl and duration of infusion or PNA. They also determined the MR, a surrogate measure of CYP3A activity, as being higher than previous reports in (pre)term neonates and attribute this to a reduced renal elimination Cl of the metabolite. Similarly, in the study of Ahsman et al.[31], it was shown that the Vd increased. But unlike Mulla et al.[30], they stated that Cl increased 3-fold within the first 5 days. It is estimated that this is due to the difference in the ECMO circuit construction (oxygenator). Ahsman et al.[31] also reported that concomitant inotropic infusion increased hydroxy-midazolam glucuronide Cl by 23% and midazolam dose could be increased starting from the 5th day.

Clonidine

Clonidine is used for sedation in the critically ill paediatric patients. However, clonidine during ECMO cannot be effectively titrated as PK parameter are lacking in neonates and infants. For this reason, Kleiber et al.[32] was aimed to describe clonidine PK in a particular ECMO system and propose dosing guidelines for children on this particular ECMO circuits. Clonidine Cl levels in children older than one month were double those found in patients not on ECMO. Furthermore, clearance rose sharply with postnatal age, reaching 30%, 50%, and 70% of the adult clearance rate at days 6, 8, and 10, respectively. During ECMO assistance, Vd rose by 55%. As a consequence, the maximum suggested bolus dosage was 5 g/kg, and the authors

simulated the number of 5 g/kg bolus doses required to attain the goal concentration of 2 ng/ml within 1 h, and three repeated 5 g/kg bolus doses were required (Table 9).

Morphine

Two articles on the same population evaluating the PK of morphine and its metabolites in neonates undergoing ECMO were retained by the same authors.[33,17] In the first study, morphine Cl was lower in neonates [postnatal age (PNA) 7 days] at the start of ECMO (2.2 l per hour per 70 kg) than in postoperative neonates (10.5 l per hour per 70 kg), but rapidly increased (maturation $t_{1/2}$ 30 and 70 days, respectively) to equal that of the postoperative group after 14 days. The authors stated that Cl was affected by size and age only and that Vd increased with age and was 2.5 times higher in neonates undergoing ECMO than in postoperative cases. Similar to the findings on phenobarbital, the coefficient of variation was significantly higher in neonates on ECMO when compared to postoperative cases.[17 34] Morphine-3-glucuronide (M3G) was the primary metabolite. In the study evaluating the PK of M3G, elimination Cl of M3G was lower in the neonates on ECMO, attributed to reduced renal elimination clearance. These elimination clearances were correlated positively with ECMO flow and negatively correlated with dopamine dose.[17] However, Peters et al. suggested that dopamine needs very likely is not causally associated with decreased clearance, but rather a reflection of poorer circulation[17] (Table 10).

Peters et al.[33] found that morphine Cl on ECMO lags behind that in healthy postoperative neonates of the same age but matures rapidly and was similar to the cohort of postoperative surgical neonates within two weeks. After this study, on the contrary, the same authors found that formation Cl to M3G is reduced during the first ten days of ECMO with the same study population.[17]

Others

Phenobarbital

Phenobarbital is an anticonvulsant still commonly used in neonates and infants undergoing ECMO to treat seizures (18-20%) and withdrawal symptoms, with midazolam as a commonly used second-line drug to treat seizures or to sedate the newborn.[35] The distribution of phenobarbital, a lipophilic drug, was not affected by ECMO as the sodium salt formulation has

good water solubility (logP= 1.77). In contrast, it was shown in two studies that the distribution of midazolam increased. Pokorná et al.[35] found similar high inter-individual PK variability for Vd and Cl and no statistical differences in Vd or Cl. The authors assumed that the physicochemical characteristics of phenobarbital resulted in differences in the distribution in comparison with ECMO-induced changes for typical lipophilic drugs. Michaličková et al.[34] found that the phenobarbital Cl increased in the time interval (day 1-12) studied within 12 days. Different loading and maintenance doses were used in both studies, and different Vd and Cl values were calculated. Because of the substantial unexplained variability, individual patients should consider regular and recurrent therapeutic drug monitoring and therapeutic concentration intervention, even with the model-derived regimen.[34]

Body weight was the main PK covariate of phenobarbital disposition.[35] In the study by Michaličková et al., the Vd of phenobarbital was not much affected by ECMO, while its Cl increased over time, especially in the first 12 days.[34] Both (body weight and postnatal age) rather reflect maturational covariates. Furthermore, there was still high unexplained variability.[34] In both studies, the suggested target range for phenobarbital therapeutic concentration was 10-40 mg/L.

Thibault et al.[36] created a popPK model for IV phenobarbital in neonates following cardiac surgery and ran simulations to find the optimal dose regimes. Loading doses of 30 and 20 mg/kg reached target concentration with albumin levels less than or equal to 3 and 3.5 mg/dL, respectively, in neonates not on ECMO. Also, loading doses of 30 mg/kg were effective on ECMO independent of albumin levels. In addition, all neonates attained target concentrations with maintenance doses of 4-5 mg/kg/d. The purpose of this study was to assess the effect of changed protein binding or, more likely, positive fluid balance in phenobarbital dosing (Table 11).

Theophylline

According to the Mulla et al.[37] study that determined popPK for theophylline during ECMO from routine monitoring data, the estimated Cl is significantly lower, and Vd higher, than previously reported in non-ECMO patients of similar age. These variations are most likely due to the increased circulation volume during ECMO as well as decreased renal and hepatic function in this population. The high inter-individual variability reflects the varied character of ECMO patients (Table 12).

DISCUSSION

Most of the studies included in the review were on antimicrobials including vancomycin, meropenem, fluconazole, gentamicin, cefotaxim, and cefepim. This confirm the pattern on drug utilization described by Buck et al in 2003[9] both drugs are hydrophilic, have a rather low Vd (L/kg) and a narrow therapeutic range. Vd relates the amount of drug in the body to the plasma concentration of the drugs, depending on the fluid in which concentration is measured.[38] Vd depends on substance characteristics and patient factors which can be different between neonates and adults.

In this literature review, because drug clearance is difficult to predict because of dynamic ontogenetic changes in renal function, ECMO received neonates and infants without concomitantly CRRT included to avoid heterogeneity.[39] Therefore, target concentration intervention based on serum concentrations is indispensable to ensure therapeutic exposure in this population.

Most studies found that patients undergoing ECMO had higher Vd and lower Cl than non-ECMO patients. The PK differences in which we have the highest confidence are from trials that included non-ECMO comparison groups. However, the bulk of the studies, did not include non-ECMO comparator groups, and the comparisons were based on PK data provided in other published data.[40] The differences in Vd and Cl of some of the studied drugs, such as vancomycin, between ECMO and non-ECMO controls demonstrated significant intra-study variability, with some studies showing increased values for the PK parameters[31 32 36], while others showed decreased values or no change.[23 24 41]

In this literature review, most studies evaluated both VV and VA modalities of ECMO together. According to the Bhatt-Mehta et al.[42] study, there was no statistically significant between VA and VV bypass type in terms of Vd (0.61 ± 0.15 vs. 0.74 ± 0.23 L/kg), Cl (0.157 ± 0.046 vs. 0.199 ± 0.085 L/h), and $t_{1/2}$ (10.04 ± 2.45 vs. 10.75 ± 3.43 h) ($p>0.05$).[42] Therefore, it is estimated that none of the included studies analyzed the VV-VA difference in terms of PK parameters.

In general, changes in tissue distribution caused by a severe illness are more likely to be clinically important for hydrophilic drugs that lack meaningful intracellular penetration and so have a low Vd.[43] Also, because neonates have a larger proportion of body water, the Vd per

kg for water-soluble substances may be higher.[44] In addition to all these factors, it is reasonable to expect that the Vd of hydrophilic drugs will increase once the ECMO circulation is connected. This can be attributed to the circuit itself, as well as to the additional capillary leak commonly observed in these patients. To further illustrate this, all studies examining vancomycin and gentamicin consistently showed an increased Vd in neonates undergoing ECMO.[8 9]

Critical illness may significantly affect dexmedetomidine PK, mainly through decreased hepatic metabolism and elevated Vd induced by organ failure and inflammation, which may be modified further by the presence of ECMO. Increases in Cl result in higher dexmedetomidine concentrations, while increases in Vd result in lower concentrations. According to the Thibault et al.,[45] Exploration of PK data using previously published models resulted in overprediction of observed values, which might have theoretically suggested higher Vd and Cl. Adding a component on Vd, on the other hand, did not enhance their goodness of fit plots, implying that increasing Vd does not explain their findings. This study found that popPK models that are relevant to a wide range of ages and diseases are more feasible in paediatric critical care settings but more difficult to design.

As a final reflection, we wanted to mention that we could not retrieve reports on any subsequent validation study for the adapted dosing regimens suggested. Furthermore, the reporting on toxicity and safety in these population PK studies is not present in these papers, so that additional studies to validate the adapted dosing regimens on efficacy and toxicity are warranted.[41] From a methodological perspective, better descriptions on the pathophysiology over time can be very useful to feed (patho)physiology-based PK models as illustrated for fluconazole PK over the human age span, including neonates.[8 46] Previously, Hoie et al.[47] had recommended a vancomycin dose of 20 mg/kg at an 18-h interval for infants on ECMO with serum creatinine levels of <1.5 mg/dl. However, Amaker et al.[41] data indicate that infants on ECMO with serum creatinine levels of <1.5 mg/dl should be given vancomycin no more frequently than every 24 h. In comparison with previously published data, the neonates undergoing ECMO in this study demonstrated a much larger Vd, a lower Cl, and a longer $t_{1/2}$ with an individual PK study.

This paper has its strengths and limitations. The predefined approach to focus on population PK studies has limitations, but these methods does provide the best approach to analysis trends over time, as well as covariates involved. Furthermore, the search strategy was structured, but not compliant with all guidelines (like number of databases searched) relevant for a meta-analysis.

CONCLUSION

The aim of this paper was to determine the effect of ECMO use on PK in neonates, based on a systematic assessment of population PK studies. At present, there are a limited number of population PK studies for a limited number of compounds reported in neonates undergoing ECMO. Despite some differences in results for the same drug, the general pattern suggests an increase in Vd and $t_{1/2}$, a stable to decreased Cl, and an increase in intra- and interpatient variability on ECMO. There was no any relevant toxicity and safety parameters reported, including in those studies with more than 100% increased PK parameters. Therefore, we recommend more studies are needed to address this toxicity and safety concern. Consequently, and if possible, therapeutic drug monitoring and target concentration intervention are strongly recommended to determine the appropriate exposure and doses for neonates undergoing ECMO.

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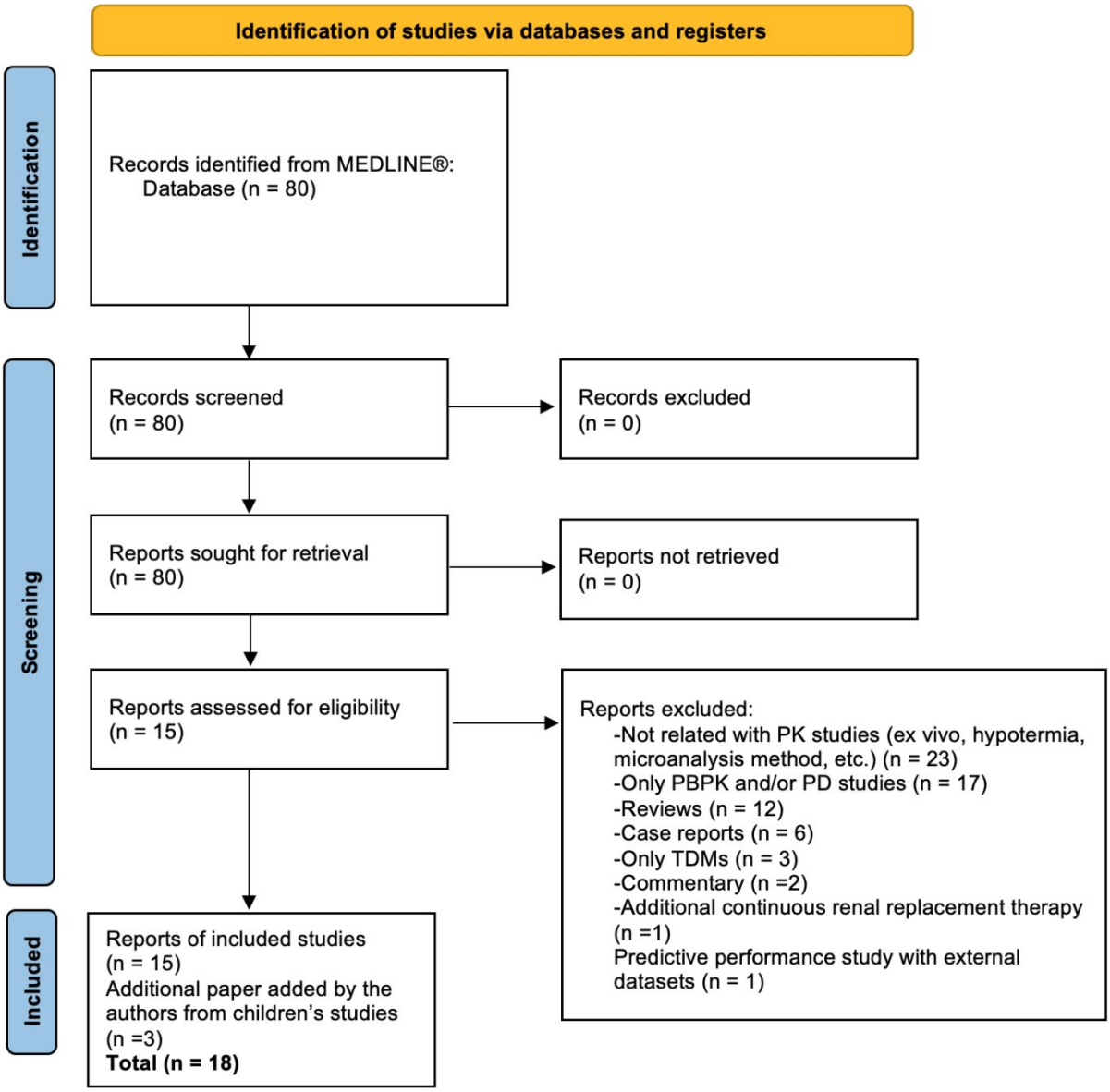
Figure 1. PRISMA flow diagram of data selection and subsequent results



MEDLINE: Medical Literature Analysis and Retrieval System Online, PK: Pharmacokinetics, PBPK: Physiologically based pharmacokinetic modelling, PD: Pharmacodynamics, TDM: Therapeutic drug monitoring

Table 1. Study characteristics (N=18)

Characteristics	**n**
Type of Study	
Prospective observational	11
Retrospective observational	6
Prospective & Retrospective	1
Drug	
Vancomycin	4
Meropenem	2
Fluconazol	1
Gentamicin	2
Cefepime	2
Midazolam	2
Phenobarbital	2
Theophylline	1
Clonidine	1
Morphine	1
Cefotaxime	1
ECMO Modality	
Veno-venous	-
Veno-arterial	2
Mixed	16
Pharmacokinetic Parameters	
Absorption	-
Distribution	16
Metabolic clearance	2
Renal clearence	17

Table 2. Characteristics of the studies, pharmacokinetics, and dose recommendations related to vancomycin

Study	n	PNA	Weight	Type	Group	Model	Modality	Administered Dose	V_d	C_L	$t_{1/2}$ (hours)	Recommended Dose
*Mulla et al[21] 2005, UK**	15	8.2	3.5	P&R	children	2-comp with WinNonMix	VV-VA	10–15mg/kg q6-24h	0.45 ± 0.1 L/kg ↑	0.04± 0.02 L/kg/h ↓	10.40 ±6.67	-
*Cies et al[18] et al 2017, USA**†	12	9.5	3.1	R	neonates	1-comp with Pmetrics	VV-VA	10–15mg/kg q8-24h	1.2 ± 0.4 L/kg ↑	0.21 ± 0.08 L/kg/h ↑	14.1 ± 6.9	-
*Zylbersztajn et al[19] 2021, Chile***†		24 (2-132) months	10 (3.5-37)	P	children	2-comp with PMetrics	VV-VA	10-15 mg/kg q6-12h	0.42 ± 0.28 L/kg ↑	0.06 ± 0.05 L/kg/h ↔	-	Across each dosing interval 63.6% of patients achieved the PK/PD targets for adequate exposure.
*Moffett et al[20] 2018, USA***†	N: 28 I: 28	0.64 (0.07-6.7) years	7.6 (3.7-21.9)	R	children	2-comp with NONMEM	VV-VA	25 mg/kg q18h for neonates 30 mg/kg q12h for infants	$Vd_{central}$: 0.36 L/kg $Vd_{peripheral}$: 0.46 L/kg ↑	0.06 L/kg/h ↔	-	25–30 mg/kg/dose q12–24 h with serum concentration monitoring is a reasonable empiric dosing strategy to obtain an area under the curve for 24 h greater than 400.

N: Neonates, I: Infants, VV: Veno-venous, VA: veno-arterial, R: Retrospective, P: Prospective, LD: Loading dose, MD: Maintenance dose, CI: Continuous infusion
Boldface fonts represent comparisons to controls within the same study. In other studies, they represent comparisons to non-ECMO neonates from a different published study.
* The reference range for serum vancomycin concentrations was trough 5-15 mg/L.
** The reference range for serum vancomycin concentrations was trough >10 mg/L.
*** The reference range for serum vancomycin concentrations was trough <15 mg/L.
† De Hoog et al.'s neonatal PK data were used to compare Vd (0.57 to 0.69 L/kg) and Cl (0.04 to 0.09 L/kg/h).[48]

Table 3. Characteristics of the studies, pharmacokinetics, and dose recommendations related to meropenem

Study	n	PNA	Weight	Type	Group	Model	Modality	Administered Dose	V_d	C_L	$t_{1/2}$ (hours)	Recommended Dose
Wang et al[23] 2021, China	9*	2.00 (0.71-3.88) years	11.50 (9.50-36.30)	P	children	2-comp with first order Elimination with NONMEM	VV-VA	20-40 mg/kg q8h	-	11.59 (5.92–20.19) vs 13.51 (3.71-20.80) L/h **↓14.2% (compared to controls)** 11.59 (5.92–20.19) vs 7.9 ± 5.9 L/h ↑46.7% (compared to adults)	-	The authors recommended the opitimized dosing regimens for septic children receiving ECMO depending on the PTA of PK target 50%T > MIC and 100%T > MIC, for children with sepsis during ECMO with different body weight, estimated Cl and MIC of bacteria.
Zylbersztajn et al.[19] 2021, Chile	9	48 (2–165) months	16 (3.5–45)	P	children	2-comp with PMetrics	VV-VA	20-40 mg/kg q8-12h	0.289 ± 0.295 L/kg -	0.139 ± 0.102 L/h/kg -	-	Across each dosing interval 91% of patients achieved the PK/PD targets for adequate exposure for meropenem. Higher dosing with extended infusion were needed in the meropenem administration.

VV: Veno-venous, VA: veno-arterial, R: Retrospective, P: Prospective, LD: Loading dose, MD: Maintenance dose, CI: Continuous infusion, PTA: probability of target attainment, MIC: minimum inhibitor concentration
Boldface fonts represent comparisons to controls within the same study. In other studies, they represent comparisons to non-ECMO neonates from a different published study.
*Number of patients undergoing only ECMO circuit.

Table 4. Characteristics of the studies, pharmacokinetics, and dose recommendations of isolated studies on fluconazole

Study	n	PNA	Weight	Study design	Group	Model	Modality	Administered Dose	V_d	Cl	$t_{1/2}$ (hours)	Recommended Dose
Watt et al[24] 2015, USA	40	22	3.4	P 2-groups	infants	1-comp. with NONMEM	VV	25 mg/kg loading dose followed 12 mg/kg/day maintenance therapy	For neonates (ECMO vs. non-ECMO): 1.5 (1.3, 1.8) vs. 0.96 (0.55, 1.4) L/kg **↑56.2%** For infants (ECMO vs. non-ECMO): 1.2 (0.91, 1.6) vs. 0.83 (0.72, 1.0) L/kg **↑44.6%**	For neonates (ECMO vs. non-ECMO): 0.018 (0.013, 0.04[illegible] vs. 0.018 (0.008, 0.04[illegible] L/h/kg **↔** For infants (ECMO vs. non-ECMO): 0.022 (0.011, 0.03[illegible] 0.017 (0.008, 0.02[illegible] L/h/kg **↑29.4%**	-	12 mg/kg for prophylaxis 35 mg/kg for invasive candidiasis treatment

VV: Veno-venous, VA: veno-arterial, R: Retrospective, P: Prospective, NONMEM: Nonlinear mixed-effects modelling, LD: Loading dose, MD: Maintenance dose, CI: Continuous infusion6
Boldface fonts represent comparisons to controls within the same study. In other studies, they represent comparisons to non-ECMO neonates from a different published study

Table 5. Characteristics of the studies, pharmacokinetics, and dose recommendations related to gentamicin

Study	n	PNA	Weight	Study design	Group	Model	Modality	Administered Dose	V_d	Cl	$t_{1/2}$ (hours)	Recommended Dose
Dodge et al 1994, USA[25]	11	37-42 PMA	2.67-5.10	P 1-group	Neonates and infants	1-comp with NPEM	VV-VA	2.5 mg/kg loading dose and q8-12h maintenance dose	From 0.748 L/kg to 0.471 L/kg after ECMO was discontinued **↑58.8%**	From 0.239 L/h to 0.350 L/h after ECMO was discontinued **↓31.7%**	From 9.24 h to 3.87 h after ECMO was discontinued **↑138.7%**	4.3 mg/kg loading dose 3.7 mg/kg q18-24h maintenance dose
Moffett et al 2018, USA[22]	N: 28 I:5	0.17 (0.12 - 0.82) m	3.1 (2.4-3.8)	R 1-group	Mostly neonates and infants	2-comp with NONMEM	VV-VA	1.8 mg/kg/dose	0.60 L/kg -	0.03 L/kg/h -	-	Children with elevated serum creatinine values should have extended dosing intervals (4-5 mg(kg/day).

N: Neonates, I: Infants, VV: Veno-venous, VA: veno-arterial, R: Retrospective, P: Prospective, NPEM: Nonparametric expectation and maximization, LD: Loading dose, MD: Maintenance dose, CI: Continuous infusion
Boldface fonts represent comparisons to controls within the same study. In other studies, they represent comparisons to non-ECMO neonates from a different published study.

Table 6. Characteristics of the studies, pharmacokinetics, and dose recommendations of isolated studies on cefotaxime

Study	n	PNA	Weight	Study design	Group	Model	Modality	Administered Dose	V_d	C_L	$t_{1/2}$ (hours)	Recommended Dose
Ahsman et al[26] 2010, the Netherlands	37	3.3 (0.67-199)	3.5 (2.0-6.2)	P 1-group	neonates	1-comp. with NONMEM	VV-VA	50 mg/kg q12h (PNA<1 w) 50 mg/kg q8h (1<PNA<4 w) 37.5 mg/kg q6h (PNA>4 w)	ECMO vs. non-ECMO: 1.82 L vs. 0.68 to 1.14 L **↑59.6-167.6%**	ECMO vs. non-ECMO: 0.36 L/h vs. 0.20 to 0.55 L/h ↔	3.5 h	The standard cefotaxime dose regimen provides a sufficiently high $t_{>MIC}$ in infants undergoing ECMO.

IQR: Interquartile range, VV: Veno-venous, VA: veno-arterial, R: Retrospective, P: Prospective, NONMEM: Nonlinear mixed-effects modelling, LD: Loading dose, MD: Maintenance dose, CI: Continuous infusion, MIC: Minimum inhibitor concentration

Boldface fonts represent comparisons to controls within the same study. In other studies, they represent comparisons to non-ECMO neonates from a different published study

Table 7. Characteristics of the studies, pharmacokinetics, and dose recommendations of isolated studies on cefepime

Study	n	PNA	Weight	Study design	Group	Model	Modality	Administered Dose	V_d	CL	$t_{1/2}$ (hours)	Recommended Dose
Thibault et al[27] *2022, USA*	9/17	0.5 (0.2-2.5) m	4.4 (3.5-4.6)	P 1-group	Children	2-comp. with NONMEM	VV-VA	50 mg/kg q6-24h or 100-150 mg/kg/d continuous infusion	Vc + Vp = 0.6 L/kg	410 ml/h/4.4 kg	-	Dosing regimens of 50mg/kg q8h reached optimal concentrations at an MIC of 8mg/L based on simulations.
Zuppa et al[28] *2019, USA*	17	1.3-22 m	3.3-10	P 1-group	infants	2-comp with NONMEM	VV-VA	50 mg/kg q8-24h	Vc + Vp = 0.4 L/kg **↑250%**	7.1mL/min/3.8 kg **↓26.6%**	-	For free cefepime, only 14 of the 19 doses (74%) demonstrated a *fT*_MIC of 16 mg/L, an appropriate target for the treatment of *pseudomonal* infections, for greater than 70% of the dosing interval.

IQR: Interquartile range, VV: Veno-venous, VA: veno-arterial, R: Retrospective, P: Prospective, NONMEM: Nonlinear mixed-effects modelling, LD: Loading dose, MD: Maintenance dose, CI: Continuous infusion, MIC: Minimum inhibitor concentration

Boldface fonts represent comparisons to controls within the same study. In other studies, they represent comparisons to non-ECMO neonates from a different published study

Table 8. Characteristics of the studies, pharmacokinetics, and dose recommendations related to midazolam

Study	n	PNA	Weight	Study design	Group	Model	Modality	Administered Dose	V_d	C_L	$t_{1/2}$ (hours)	Recommended Dose
Mulla et al 2003, UK[30]	19	3.8	3.4	P Random 2-groups	neonates	1-comp. with WinNonMix	VV-VA	50-250 µg /kg/h	From 0.8±0.5 to 4.1±0.5 L/kg **↑412.5%**	1.4 ± 015 mL/kg -	From 6.8 (2.2–39.8) to 33.3 (7.4-178) **↑389.7%**	LD: 350 µg /kg/h for 6 hours MD: 50 µg /kg/h
Ahsman et al[31] *et al 2010, the Netherlands*	20	0.79	3.0	P 1-group	neonates	A two-compartment model for midazolam and a one-compartment model for the metabolites with NONMEM	VA	LD: 0.2 mg/kg bolus MD: 0.1 mg/kg/h CI	Midazolam: 14.6 L/3kg 1-hydroxymidazolam: 10.2 L/3 kg Hydroxymidazolam glucuronide: 1.21 L/3 kg **↑240.3%**	Midazolam: 1.38 L/h/3 kg 1-hydroxymidazolam: 1.03 L/h/3 kg Hydroxymidazolam glucuronide: 0.18 L/h/3 kg **↑300.0%**	1.85 -	LD: 300 µg /kg/h for 6 hours MD: 150 µg /kg/h

VV: Veno-venous, VA: veno-arterial, R: Retrospective, P: Prospective, NONMEM: Nonlinear mixed-effects modelling, LD: Loading dose, MD: Maintenance dose, CI: Continuous infusion
Boldface fonts represent comparisons to controls within the same study. In other studies, they represent comparisons to non-ECMO neonates from a different published study.

Table 9. Characteristics of the studies, pharmacokinetics, and dose recommendations of isolated studies on clonidine

Study	n	PNA	Weight	Study design	Group	Model	Modality	Administered Dose	V_d	C_L	$t_{1/2}$ (hours)	Recommended Dose
Kleiber et al[32] 2017, the Netherlands	22	1 (IQR 6.4) m	4 (IQR 3.1)	P 2-groups	Children	1-comp. with NONMEM	VV-VA	0.24 (0.15) µg/kg/h infusion	454 L/70 kg at ECMO start **↑55%**	29.9 L/h/70 kg at ECMO start **↑200%**	-	The authors simulated the number of bolus doses of 5 µg/kg needed to reach the target concentration of 2 ng/ml within 1 h: three repeated bolus doses of 5 µg/kg were needed.

IQR: Interquartile range, VV: Veno-venous, VA: veno-arterial, R: Retrospective, P: Prospective, NONMEM: Nonlinear mixed-effects modelling, LD: Loading dose, MD: Maintenance dose, CI: Continuous infusion6
Boldface fonts represent comparisons to controls within the same study. In other studies, they represent comparisons to non-ECMO neonates from a different published study

Table 10. Characteristics of the studies, pharmacokinetics, and dose recommendations of isolated studies on morphine

Study	n	PNA	Weight	Study design	Group	Model	Modality	Administered Dose	V_d	Cl	$t_{1/2}$ (hours)	Recommended Dose
Peters et al[33] 2005, the Netherlands	14	82	4.2	P	infants	1-comp. with NONMEM	VA	LD: 100 µg /kg MD: 40 µg /kg/h	Day 1: 1.89 mL/kg/min Day 10: 3.33 mL/kg/min **↑76.2%**	Day 1: 1.1 mL/kg/min Day 10: 6.0 mL/kg/min **↑445.5%**	-	Serum concentrations decrease during the first 10 days of ECMO, and that dose adjustments should be carried out.

VV: Veno-venous, VA: veno-arterial, R: Retrospective, P: Prospective, LD: Loading dose, MD: Maintenance dose, CI: Continuous infusion6
Boldface fonts represent comparisons to controls within the same study. In other studies, they represent comparisons to non-ECMO neonates from a different published study

Table 11. Characteristics of the studies, pharmacokinetics, and dose recommendations related to phenobarbital

Study	n	PNA	Weight	Type	Group	Model	Modality	Administered Dose	V_d	C_L	$t_{1/2}$ (hours)	Recommended Dose
Michaličková et al[34] et al 2020, Czech Republic	13	2	3.21	R	neonates	1-comp with NONMEM	VV-VA	LD: 7.5mg/kg (8.5–16mg/kg) MD: 6.9mg/kg/d (4.5–8.5 mg/kg/d).	2.72 L	0.0096 L/h	-	In the first 12 days of ECMO with a regimen of a LD of 20 mg/kg and a MD of 4 mg/kg/d divided in two doses with an increase of 0.25 mg/kg every 12 hours during ECMO
Thibault et al[36] 2020, USA	12/37*	5 (0-26)	3.2 (1.3-3.8)	R	neonates	1-comp with first-order elimination with NONMEM	VV-VA	LD: 15-20 mg/kg MD: 3-6 mg/kg/d	**↑22%** (Normalization of albumin values from 2.5 mg/dL to 3.5 mg/dL decreased the estimated V by 13%)	**↑114%** (Over the first 20 days of life)	-	LD 30 mg/kg achieved goal peak concentration. MD of 4-5 mg/kg/d sustained goal trough concentration

VV: Veno-venous, VA: veno-arterial, R: Retrospective, P: Prospective, LD: Loading dose, MD: Maintenance dose, CI: Continuous infusion
Boldface fonts represent comparisons to controls within the same study. In other studies, they represent comparisons to non-ECMO neonates from a different published study.
*Number of patients undergoing only ECMO circuit.

Table 12. Characteristics of the studies, pharmacokinetics, and dose recommendations related to theophylline

Study	n	PNA	Weight	Study design	Group	Model	Modality	Administered Dose	V_d	C_L	$t_{1/2}$ (hours)	Recommended Dose
Mulla et al[37] 2003, UK	N: 38 I: 14	8.4 ± 5.9 for neonates 122 ± 107 for infants	3.3 ± 0.5 for neonates 4.8 ± 2.0 for infants	R 1-group compared with the literature	Children	1-comp. with first order elimination with Win-NonMix Professional	VV-VA	9.2 ± 2.6 µg/kg/min infusion	The interindividual variability **↑40%**	The interindividual variability **↓38%**	-	Maintenance infusion rates following an initial loading dose (0.57 x weight (kg) x 10 mg/L). Maintenance infusion rate calculated from: average steady-state concentration = rate of infusion/clearance (using clearance parameters determined in the final model).

N: Neonates, I: Infants, VV: Veno-venous, VA: veno-arterial, R: Retrospective, P: Prospective, NONMEM: Nonlinear mixed-effects modelling, LD: Loading dose, MD: Maintenance dose, CI: Continuous infusion6
Boldface fonts represent comparisons to controls within the same study. In other studies, they represent comparisons to non-ECMO neonates from a different published study