

A systematic review on pharmacokinetic changes in critically ill patients: role of extracorporeal membrane oxygenation

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ABSTRACT

Objective: Several factors including disease condition and different procedures could alter pharmacokinetic profile of drugs in critically ill patients. For optimizing patient's outcome, changing in dosing regimen is necessary. Extracorporeal Membrane Oxygenation (ECMO) is one of the procedures which could change pharmacokinetic parameters. The aim of this review was to evaluate the effect of ECMO support on pharmacokinetic parameters and subsequently pharmacotherapy.

Method: A systematic review was conducted by reviewing all papers found by searching following key words; extracorporeal membrane oxygenation, ECMO, pharmacokinetic and pharmacotherapy in bibliography database.

Results: Different drug classes have been studied; mostly antibiotics. Almost all of the studies have been performed in neonates (as a case series). ECMO support is associated with altered pharmacokinetic parameters that may result in acute changes in plasma concentrations with potentially unpredictable pharmacological effect. Alteration in volume of distribution, protein binding, renal or hepatic clearance and sequestration of drugs by ECMO circuit may result in higher or lower doses requirement during ECMO. As yet, definite dosing guideline is not available.

ECMO is extensively used recently for therapy and as a procedure affects pharmacokinetics profile along with other factors in critically ill patients. For optimizing the pharmacodynamic response and outcome of patients, drug regimen should be individualized through therapeutic drug monitoring whenever possible.

Keywords: Extracorporeal membrane oxygenation (ECMO), Pharmacokinetics, Systematic review.

INTRODUCTION

Extracorporeal Membrane Oxygenation (ECMO) is an advanced life support system for providing respiratory and cardiorespiratory support for patients of all ages who have failed conventional intensive care management. This technique was adopted from cardiopulmonary bypass used in open heart surgery and provides passive support of gas exchange and perfusion, thereby allowing implementation and optimisation of other forms of therapy to aid organ recovery (1-3). Extracorporeal lung assist (ECLA), extracorporeal life support (ECLS), and extracorporeal CO₂ removal (ECCOR) are other synonyms of ECMO.

A variety of diagnosis, including Meconium Aspiration Syndrome (MAS), congenital diaphragmatic hernia (CDH), persistent pulmonary hypertension of the newborn (PPHN), respiratory distress syndrome, cardiac anomaly, sepsis or

pneumonia are the reasons for performing ECMO in neonates (4-6). Use of ECMO in adult patients both as a treatment for acute respiratory and cardiorespiratory failure or as a bridge to either cardiac transplantation or placement of a ventricular assist device is necessary (7-11).

In the cases of irreversible respiratory or cardiac failure and any contraindication for anticoagulation, ECMO should not be started. Advanced age, morbid obesity, neurologic dysfunction or poor pre-existing functional status are other exclusion conditions (7; 12).

There are two types of ECMO-Venoarterial (VA) and Venovenous (VV). Generally during ECMO, a large volume of blood is extracted from the venous system (large central vein) and circulated outside the body by a mechanical pump (centrifugal or roller), where the blood passes through an oxygenator and heat exchanger. In the oxygenator, hemoglobin becomes

fully saturated with oxygen, while CO₂ is removed. Finally the blood is returned into the native vascular system (venous system near the right atrium in VV and arterial system in the aorta in VA ECMO) (3; 13).

In VV ECMO the circulation is powered entirely by native cardiac function, so it just provides support for respiratory failure, but in VA ECMO blood bypassing the heart and lungs, so it can be used for both respiratory and cardiac failures. Avoiding arterial cannulation and maintaining pulsatile blood flow to the patient are other advantages of VV ECMO (2; 11; 13).

Depending on diagnosis and age group, ECMO increase survival rate to 50-95% in comparison with conventional treatment such as mechanical ventilation with high inspired fractional oxygen or instillation of surfactant. Survival rate for children requiring ECMO for respiratory support is 63%, for children needing cardiac support is 55% and for adults it is nearly 50 % (14-17).

Critically ill patient's exhibit a range of organ dysfunctions and often require therapeutic support with a variety of procedures including mechanical ventilation and renal replacement therapy. These procedures along with underlying pathophysiological process result in changes in major pharmacokinetic parameters such as volume of distribution (Vd) and clearance (CL) in critically ill patients (18-28). Several aspects of ECMO (as a procedure in ICU) such as sequestration of drug by ECMO circuit, increase in the volume of distribution, alteration in renal and hepatic blood flow, flow rate of the system and other factors change pharmacokinetic parameters of drugs (13; 29-34). Of different drug classes some of them such as sedative (propofol) (35) or vasopressors (norepinephrine) (36) could be easily titrated according to patient's response but for others especially antibiotics (cefepim, vancomycin) (37, 38) titration of dose based on patient response rate is not possible, thus applying pharmacokinetic principles in selection of drug and dosing regimen is crucial for optimization the pharmacodynamic response and outcome of patients.

The aim of this study is to review the effect of ECMO support on pharmacokinetic parameters and optimal dosing regimen during ECMO.

METHODS

In order to provide enough databases about the subject, a systematic search utilizing Pubmed, Scopus, Google Scholar and Embase database was carried out. The initial search terms were "extracorporeal membrane oxygenation", "ECMO", pharmacokinetic and pharmacotherapy, without narrowing or limiting search elements to find the most relevant literatures about the subject. References from each article were also evaluated for

relevancy of inclusion in the study. All papers were reviewed to omit irrelevant or duplicate papers, and then their data were extracted into tables and summarized.

RESULTS AND DISCUSSION

As summarized in table 1, different drug classes have been studied in patients under ECMO. Almost all of these studies were performed in neonates and usually without control groups and on the basis of pharmacokinetic parameters such as volume of distribution, clearance and half life a dose or method for monitoring was recommended. Small sample size, differences in ECMO technique and equipment, complexity of patients with lack of uniform diagnosis, different methods for evaluation of kinetic were limitations of these studies which complicate clinical judgment. Also due to inadequate investigation, definite recommendation for adults is not possible. Antibiotics, sedatives, analgesics, anticonvulsants are the most studied drugs in patients under ECMO (Table 1).

Mixing of priming volume with the patient's own blood volume increase effective circulating volume and decrease in the total blood concentration is the immediate effect of this acute hemodilution (13; 29). The pharmacological impact depend on the apparent Vd of the drugs, the degree of protein binding and the extent of equilibration between tissue and plasma concentrations on initiation of ECMO (13; 34; 39). Drugs with large Vd e.g. amiodarone (40) would be expected to show only a slight changes because drug back diffuse to plasma from large tissue reservoirs. In contrast, a drug with a small Vd such as gentamicin may be significantly affected and the resultant enlarged apparent Vd may affect the elimination rate of the drug. Depletion of the plasma protein such as albumin during acute hemodilution may affect plasma and tissue protein binding and plasma concentrations of drugs, but it is just a transient effect because transfusing blood and related products such as albumin will normalize the effects of hemodilution (39).

Changes in blood flow affect clearance of drugs during ECMO. VV ECMO result in pulsatile blood flow, whereas VA ECMO at high flow rates (>100ml/kg/min) may produce non-pulsatile flow. Non-pulsatile flow can alter perfusion of tissues, reduce capillary circulation and aerobic metabolism (41; 42). The kidneys interpret pulsless blood flow as hypotension and activate the renin-angiotensin system which result in reduced urine production and impaired sodium excretion. Regional blood flow changes in the liver can also affect drug clearance, in particular those drugs with a high extraction ratio e.g. propranolol (43). Perfusion of tissues may also be altered as a result of activation of Systemic Inflammatory Response System (SIRS) releasing a variety of autonomic, endocrine and local cytokine

that may affect not only tissue distribution of drugs but also clearance mechanism as well.

The loss of drugs to the ECMO circuit (to tube or oxygenator) depend on the surface area in contact with the circulating fluid and extent of any physiochemical interactions between individual drugs and the different plastic components of the circuit (31, 44). Based on studies for evaluation of drug sequestration during ECMO, significant sequestration of opioids (alfentanil, fentanyl, morphine), benzodiazepins (midazolam, diazepam, lorazepam), glyceryl nitrate and propofol, has been reported and it has also been described that ECMO circuit decrease levels of phenobarbital, heparin, vancomycin, gentamicin and phenytoin delivery (31; 44; 45). Voriconazol, cefazolin and ampicillin are also sequestered during ECMO and therefore their therapeutic concentrations cannot be definite. Gentamicin is the most well studied drug in patients under ECMO (table 1). All of studies on gentamicin have been performed on neonates. None of studies had control groups and only pharmacokinetic parameters have been compared before and after stopping ECMO. Usually dose rate of 2.5 mg/kg every 12 hrs was administered for infants under ECMO, blood samples were collected after steady state (usually 3 days), pharmacokinetic parameters were evaluated and correlation between ages, weight, and serum creatinin had been evaluated. Cohn et al. (59) compared data for patients on ECMO and after discontinuation of ECMO. They reported significant increase in Vd and half life and decrease in clearance for patients on ECMO and a dose rates of about 25% lower than usual and longer dosing intervals for patients undergoing ECMO therapy. A retrospective study on 29 neonates receiving gentamicin during ECMO and a comparison of kinetic parameters with non-ECMO population showed that Vd (0.66 ± 0.2 L/kg) was median in ECMO groups in comparison with non-ECMO patients ($0.58-0.75$ L/kg) but half life increased significantly during ECMO (10.4 hour) (57). According to results of all studies on gentamicin during ECMO (table 1), Vd was significantly higher and clearance was significantly lower in comparison with non-ECMO patients; because ECMO especially non-pulsatile method results in decrease of renal blood flow and Glomerular Filtration Rate (GFR) and finally reduction in renal clearance. Gentamicin is a hydrophilic drug and increase in extracellular volume following ECMO result in an increase in Vd. To achieve therapeutic levels, a maintenance dose of 2.5 mg/kg every 18 hours was recommended in neonates without renal impairment.

Vancomycin pharmacokinetic during ECMO has also been described. Buck et al. (54) conducted a retrospective study in 15 neonates who received vancomycin during ECMO and compared

pharmacokinetic data with matched control. The most frequent regimens prescribed in both groups were 10 mg/kg every 8 hrs. The data was analysed using a one compartment model and showed a Vd of 0.45 ± 0.18 L/kg, half life of 8.29 ± 2.23 hrs and CL of 0.79 L/kg/h in ECMO neonates. The parameters were not significantly different in the control group but half life was shorter. The author recommended that empiric vancomycin regimens incorporate a longer dosing interval than the 6-8 hrs which is commonly recommended for the infants. Results of other studies compared kinetic parameters with non-ECMO population show that Vd and half life were higher and clearance was lower in ECMO patients. However Hoie et al. (53) reported no difference in kinetic profile. In all above studies the numbers of neonates were small (6-12 neonates). In one study conducted in adults, there were no significant differences in pharmacokinetic parameters between ECMO and non-ECMO groups (56). Therefore due to differences in methods and populations, recommendation of a dosing regimen is not possible especially in adults.

In other studies on antibiotic in ECMO patients, despite higher Vd in ECMO patients, standard dose of cefotaxime was recommended in neonates under ECMO (61). Monitoring the level of voriconazol in patients under ECMO has been suggested because this drug is sequestered during ECMO. Caspofungin could be prescribed with the same dosage in ECMO patients (63).

Sedatives and analgesics are important classes of drugs which are extensively used in critically ill especially ECMO patients. For short term procedure fentanyl may be suitable for analgesia because this drug is extensively bind to ECMO circuit after 24 hrs and usually higher doses are required to achieve desired therapeutic effect during ECMO. In comparison, morphine concentrations were well preserved during ECMO in both crystalloid or blood primed circuit, therefore it is a preferred drug for prolonged period, However results of a study (47) has shown that morphine clearance which decreases (even to half) during ECMO leads to an increase in serum concentration and some neonates experience withdrawal syndrome after ECMO discontinuation, authors suggested that increase in hepatic blood flow might be a reason for decrease in clearance. On the other hand Jeroen et al. (66) concluded that morphine clearance was lower than non ECMO but increased rapidly and after 14 days was equal to the control group. Size and age are factors that significantly affect morphine clearance but pump flow or simultaneous drugs have no effect. Although initial morphine dosing may be guided by age and weight, but clearance and Vd change during prolonged ECMO which suggest that morphine therapy should be subsequently guided by clinical monitoring(46-48). However morphine clearance

Table 1. Pharmacokinetic changes during ECMO.

Reference	Drug	Population	ECMO	Dose/interval	Vd (L/kg)	Clearance ml/min/kg	Clearance L/kg/hr	half life(h)	Recommended Dose	Conclusion
52	Vancomycin	12 Neonates	ON* OFF NON	15 or 20mg/kg q8,12 or 18h	1.1±0.5 0.69	0.78±0.19 1.18		16.9±9.54 6.7	20 mg/kg q 24h in patients without renal impairment	Larger Vd, Lower CL, Longer half life in ECMO pt.
53	Vancomycin	6 Neonates	ON* OFF NON*	15 mg/kg q 12h	0.68±0.12	1.10±0.32		7.71±2.61	20 mg/kg q 18 h in patients without renal impairment	Difficult to compare result with other studies
54	Vancomycin	15 Neonates	ON* OFF NON	10 mg/kg q 8h	0.45±0.18 0.39±0.12	0.65±0.28	0.79±0.41	8.29±2.23 6.53±2.05	20 mg/kg q 24 h	Trends toward larger Vd and slower CL in ECMO patients
55	Vancomycin	45 mixed	ON* OFF NON	10-15mg/kg q 6-24h in children 750-1000 mg q12-24 h in adults	0.45-0.36(0.71)		0.05(overall)	8.44	20 mg/kg q 6-24h depend on StCr	Decreased CL and increased Vd in ECMO patients
56	Vancomycin	12 adults(> 18 years)	ON* OFF NON*	based on redvoid method for ClCr>50 ml/min: 1 gr q 12 h	0.84±0.24 0.83 ± 0.3	1.18 ± 0.71 1.45± 0.82		11.13±9.08 10.15±9.08	calculate dose based on this equation CL: 0.019 ClCr (ml/min/kg) - 0.18 Vd: CL*60/(K*1000 (L/kg) K:0.0017ClCr (ml/min/1.73m2) - 0.029	No significant differences in pharmacokinetics parameters between groups.
57	Gentamicin	29 Neonates	ON* OFF NON	2.5 mg/kg q 12h	0.668±0.2		0.05±0.02	10.3±2.95	2.5 mg/kg q 18 hours in patients without renal impairment	Median Vd but longer half life in comparison with other ECMO studies
58	Gentamicin	10 Neonates	ON* OFF NON	2 mg/kg q 12 h	0.51±0.11	2.78± 1.55 ml/min		57.3±263 min	2.4 ±0.5 mg/kg q 18.8 ± 8 h	Longer half life in ECMO patients
59	Gentamicin	18 on and 12 off ECMO Neonates	ON* OFF* NON	2.3± 0.1 mg/kg q 18 ± 1	0.58±0.04 0.45±0.02	42±3 57±4 (ml/kg/h)		10±0.7 5.7±0.4	depend on weight and Cr: for wt> 3.5 kg and Cr< 0.7 3 mg/kg q 18 h	Vd was significantly larger and CL was significantly lower and half life was larger in ECMO patients. Generally 25% lower dose and larger interval are needed in ECMO patients.
60	Gentamicin	11 Neonates	ON* OFF* NON	2.5 mg/kg q 12h	0.748 0.471	0.239 L/h 0.350 L/h		9.24 3.87	LD:4.3 mg/kg MD: 3.7 mg/kg q 18-24h	Higher Vd, Lower CL and longer half life in ECMO patients.

Table 1. Continue

Reference	Drug	Population	ECMO	Dose/interval	Vd (L/kg)	Clearance ml/min/kg	Clearance L/kg/hr	half life(h)	Recommended Dose	Conclusion
61	Cefotaxime	37 Neonates	ON* OFF NON	depend on age: 50 mg/kg q 8-12 h >4 wk: 37.5 mg/kg q6h	1.82 L 0.68-1.14 L	0.36 L/h 0.20-0.55 L/h		3.5 h	Standard cefotaxime dose	Higher Vd (100% increase) but similar CL in ECMO patients
62	Oseltamivir	3 mixed	ON* OFF NON	>40kg: 60 mg q 12h <15 kg: 30 mg q 12h	-	-	-	-	-	No changes in comparison with non ECMO pt.
63	Caspofungin	1	ON* OFF NON	70 mg/d	8.22 L	6.9 ml/min		13.6	-	-
64	Voriconazol	1	ON* OFF* NON	400 mg /d	1.38 1.58	49.3 47.9 ml/min		21 24	-	Voriconazol was sequestered during ECMO, so monitor the plasma level of this drug
64	Theophylline	75 Neonates	ON* OFF NON	5-15mg/kg/min without LD	0.57*BW	0.023*BW+0.000057*AGE(day)		-	Decrease MD infusion rate	Estimated CL was lower and Vd was higher compare with non ECMO.
65	Tobramycin	10 sheep	ON* OFF* NON	5mg/kg/day	0.5±0.2 0.3±0.1	1.8±0.8		2.7±0.8 1.8±0.3	Dose should be increased without any change in interval	Vd and half life increased significantly during ECMO. CL were unaffected. Tobramycin didn't sequester by ECMO circuit.
66	Morphine	14 Neonates	ON* OFF NON	LD: 100mcg/kg MD: 20 mcg/kg/h	1.89(day1) 3.33(day 10)	1.1(day 1) 6 (day 10)		-	Morphine therapy should be monitored.	CL is equal to general population after 14 days' was 2.5 times greater in ECMO patients
47	Morphine	7 Neonates	ON* OFF* NON	20-40 mcg/kg/h	-	-	0.57±0.3 1.058±0.7	-	-	After cessation of ECMO, higher dose of morphine is required
49	Midazolam	20 Neonates	ON* OFF NON	100 -300 mcg/kg/h	14.6/3 kg 4.29L/3 kg(metabolite)		5.3L/h/3kg 1.38L/h/3kg(metabolite)		300 mcg/kg/h for 6 hours then 150 mcg/kg/h	The CL and Vd of midazolam and 1-hydroxy midazolam increased during ECMO.
68	Midazolam	20 Neonates	ON* OFF NON	50-250mcg/kg/h	0.81±0.5 L/kg	1.4±0.15		6.8	-	Significant increase in Vd and plasma half life in neonates under ECMO.

Table 1. Continue

Reference	Drug	Population	ECMO	Dose/interval	Vd (L/kg)	Clearance ml/min/kg	Clearance L/kg/hr	half life(h)	Recommended Dose	Conclusion
69	Phenobarbital	1 Neonates (case report)	ON* OFF NON	LD: 20 mg/kg MD: 5mg/kg/d	1.2	-	-	92	Larger LD and MD	Vd is slightly larger and half life was similar to other studies.
70	Furosemide	31 Neonates	ON* OFF NON	median:0.08mg/kg/h different regiment	-	-	-	-	-	Regiment achieved adequate U/O. No significant differences in U/O or in time between pts.
71	Bumetanide	11 Neonates	ON* OFF NON	0.095±0.03 mg/kg	0.44 ± 0.03	-	0.038	13.2 ± 3.8	-	Increase of Vd and half life during ECMO. Significant diuresis, natriuresis and kaliuresis were observed.
51	Ramitidine	13 neonates	ON* OFF NON	2mg/kg bolus then 2mg/kg/24hr	0.25	-	1.8	6.61±2.75	2mg/kg/24hr	Continuous infusion of ranitidine for maintaining of intragastric PH above 4 is the preferred method for neonates undergoing ECMO.
72	Sildenafil	11 neonates	ON* OFF NON	1.0 mg/kg q 6 hr	34(V/F)	-	7.3 L/hr(CI/F)	-	5-7 mg/kg/24h	temporarily increased clearance (+161%) and volume of distribution (+313%) for SIL during ECMO
73	Alteplase	1 Neonates (case report)	ON* OFF NON	LD: 0.48 mg/kg MD: 0.27mg/kg/h for 8 hours	-	-	-	-	-	Additional studies to determine optimal dose and duration.
74	Prostaglandin E1	1 Neonate (case report)	ON* OFF NON	0.1 meg/kg/min	-	-	-	-	Double dose during ECMO	ECMO cause increase in Vd and decreasing in pulmonary metabolism of prostaglandin E1
75	Nicardipine	1 Neonate (case report)	ON* OFF NON	0.5 meg/kg/min then titrate to 1.5meg/kg/min	-	-	-	-	initiate with 05meg/kg/min then titrate to reduce blood pressure	Expanded Vd result in reduce serum concentration and reduced effect

Abbreviation: Vd: volume of distribution, CL: clearance, U/O: Urine Output, ECMO: Extracorporeal Membrane Oxygenation, SrCr: Serum Creatinin, ClCr: Clearance Creatinin, GFR: Glomerular Filtration Rate, ON: When patients under ECMO, OFF: After ECMO discontinuation, NON: Patients do not receiving ECMO.

in general is variable and the range of CL values exceed those which were published previously for infants who were receiving morphine.

Midazolam is also extensively used as sedative in ICU. More than 50% (a loss of 60-95% in the first hours after cannulation) of midazolam was sequestered during ECMO (PVC circuit and silicone oxygenator) so usually higher doses is required to achieve adequate sedation. Also during the first 24 hrs, because of an expanded circulating volume and sequestration by the circuit, significantly higher dose of midazolam is required to achieve adequate sedation. Ashman et al. (49) concluded that clearance of midazolam and its metabolite 1-hydroxy midazolam increased 3 folds within the first 5 days (as a result of maturation or recovery from illness) in neonates, therefore dose must be increased subsequently after 5-7 days. However large unexplained interpatient variability warrants careful titration of sedation and adverse effects of midazolam during ECMO. In conclusion, volume of distribution and clearance of midazolam are higher during ECMO, and absorptive drug loss could be a cause of higher dose requirements.

Stress ulcer prophylaxis is necessary for patients undergoing ECMO, because of the procedure by itself and simultaneous mechanical ventilation and anticoagulation. Studies with ranitidine in neonates undergoing ECMO show that in spite of greater

elimination typical dosing regimens were adequate. Also continuous infusion and combination of motility agents has been recommended in order to keep intragastric PH above 4 for prevention of upper gastrointestinal bleeding (50, 51).

Recent review on cardiovascular drug dosing in neonates under ECMO, recommended dosing modification for esmolol, amiodarone, nesiritide, bumetanid, sildenafil and prostaglandin E1, on the basis of changes in of Vd and CL of these drugs during ECMO (76) (Table 1).

CONCLUSION

Although what we have learned from the straightforward demographics (incidence of shock or renal failure, etc) are mostly clear, what we have known from drugs' fate from application of sophisticated ventilator support techniques are not very clear. In spite of considerable amount of pharmacokinetic studies during ECMO, because of small sample size, differences in methods and lack of control group, developing a guideline for dosing of drug during ECMO is difficult. Also because of potential changes in drug delivery during ECMO along with other changes in pharmacokinetic profile of critically ill patients, drug regimens should be individualized through therapeutic drug monitoring whenever possible, until further studies are carried out in this area.

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