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Pharmacology of Drugs and Their Kinetics and Dynamicity during Extracorporeal Life Support

Naman Shastri[1], Pranav Kapoor[2], Varun Kapoor[3]

[1]Chief Consultant, Cardiac Anesthesiologist and Intensivist, EPIC Hospital, Ahmedabad, Gujarat, [2]Junior Resident, House surgeon, Sharda Medical University, Uttar Pradesh, [3]Senior Consultant, Department of Orthopaedic, National Heart Institute, New Delhi, India.

***Corresponding author:**
Naman Shastri,
Chief Consultant, Cardiac Anesthesiologist and Intensivist, EPIC Hospital, Ahmedabad, Gujarat, India.

nashastri@gmail.com

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ABSTRACT

ECMO/ECLS is now a days very common modality for saving patient life in ICU. ECMO is unphysiological circulation which hampers the multiorgan function. Direct impact by releasing of pro-inflammatory cytokinin leads to impact on the many organ homeostasis. The anaesthetist/intensivist must have enough knowledge of pKa/Pd and most importantly still we do not have ideal guidelines for drug dosing.

Keywords: Drug Pharmacology, drug kinetics, ECMO, ECLS

INTRODUCTION

Extracorporeal life support is now a days very common modality for saving patient life in intensive care unit, though patient usually is on many life-saving drugs, ionotropes, antibiotics, sedation, and anticoagulation, when they are on already mechanical ventilation. Optimal pharmacotherapy helps clinicians to manage this life support modalities in better way but at the same time pharmacokinetics and pharmacodynamics of every commonly used drugs have to be understood. Using ideal dose, avoiding certain drugs by understanding Pk/Pd can reduce the iatrogenic complication. This is very important as extracorporeal membrane oxygenation (ECMO) is unphysiological circulation which hampers the multiorgan function. Direct impact by releasing of pro-inflammatory cytokinin leads to impact on the many organ homeostasis.

There are multiple effects on pharmacokinetics and dynamics LIE.

1. On drug clearance
2. Due to distribution of volume
3. Sequestration due to membrane.

DRUG CLEARENCE

Most of the data are extrapolated from the different age groups[1] and yet we do not have ideal comparable date as clearance of the drug is affected by drug distribution and metabolism by organ such as liver and kidney.[2] During initiation of the ECMO, there may be increase in cardiac output by increasing the flow and perfusion leads to increase in clearance to begin with followed by reduction.

Table 1: Summary of pharma kinetic changes and potential dosing adjustments for antimicrobials during ECMO.

Drugs	N-Octanol/water partition coefficient	Protein binding (%)	Anticipated reported pharmacokinetic changes	Dosing recommendations and comments
Antibiotics aminoglycosides	<0.0	<30	Minimal circuit drug sequestration; enlarged Vd; decreased CL	Insufficient data to recommend optimal dosing; TDM-guided dosin
Beta-lactams ampicillin	1.35	15–30	Minimal to moderate circuit drug sequestration; enlarge Vd	Consider alternatives agents; less drug loss in blood primed vs. crystalloid prime circuit
Ceftriaxone	−1.7	95	Significant circuit drug sequestration; enlarge Vd	Dosing similar to critically ill patients not on ECMO support; TDM guided dosing
Meropenem	−0.69	2	Minimal circuit drug sequestration; enlarged Vd; circuit drug loss due tostability issues associated with the carbapenems	Dosing similar to critically ill patients not on ECMO support; TDM guided dosing; consider alternatives dosing strategies (CI or EI dosing)
Piperacillin/ tazobactam	0.67	30	Minimal circuit drugs loss; enlarged Vd	Dosing similar to critically ill patients not on ECMO support; TDM guided dosing; consider alternatives dosing strategies (CI or EI dosing)
Fluoroquinolones	<2.3	20–40	Minimal circuit drugs sequestration	Dosing to optimise $AUC_{0\text{-}24}$/MIC
Vancomycin	−3.1	50–60	Minimal circuit drugs	Dosing similar to critically ill

ECMO: Extracorporeal membrane oxygenation, TDM: Therapeutic drug monitoring, AUC: Area under the curve, MIC: Minimum inhibitory concentration

SEQUESTRATION DUE TO MEMBRANE

When pharmacological properties are described, it is usually related to normal physiology, which is different than ECMO so, altering the dosing requirements is very important along with the interaction of the drug to membrane. The impact is due to both.

1. Drug characteristics
2. Membrane and circuit characteristics.

1. Drug characteristics: Certain characteristics of the drugs are very important like that need to be considered including molecular size, pKa, and degree of ionization, lipophilicity, and plasma protein binding.[3] Drugs with higher degree of lipophilicity and having high protein binding has have high chances of sequestration when they come in contact with the membrane and extracted by the ECMO circuit than drugs with a lower with lower lipophilicity.[4] Hence, both the characteristics play an important role in sequestration
2. Membrane and circuit characteristics: Initially, when patient is placed on ECMO, the total volume of the surface increases by many fold because of the tubing and membranes, so adsorption surface area increases. Once patient is maintained over few hours to days, this adsorption surface acts as reservoir and they start releasing the adsorbed molecules and this results in increasing drug concentration.[5] All these sequences depend up on the factors such as composition of the priming solution, the types of conduit and oxygenator materials [Table 1].[6]

Certain sedatives and analgesics and ECMO

Most used drug is fentanyl which is very having very high lipophilicity affinity so initially membrane sequestration is very high but over period, it starts releasing back to circuit so one should be very careful of the usage of fentanyl.[7] Dexmedetomidine also favor having high lipophilicity behave same as fentanyl. Hence, morphine proved to be better as compared to fentanyl. Nowadays, the practice of using sedation and analgesia has reduced significantly. Propofol is highly lipophilic and having high protein bound capacity which limits its use during ECMO. Furthermore, it may damage the membrane by its larger molecular size.[8]

Anticoagulants

Most preferred agent is heparin but since sequestration is very high nearly half of the heparin is sequestrated by tubing and priming and also depends up on the crystalloid and blood as they dilute and remove by 30–50% so heparin monitoring is very important.

Hence, to conclude whichever drug used during ECMO support, it is mandatory to have enough knowledge of pKa/Pd and most importantly still we do not have idea guidelines to suggest ideal dosing for different population.

Declaration of patient consent

Patient's consent not required as their identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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