Extracorporeal Mechanical Oxygenation and Drugs

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There has been a substantial increase in the use of extracorporeal membrane oxygenation (ECMO) support in critically ill adults. Critically ill patients on ECMO represent a challenging clinical situation to manage pharmacotherapy. Thus, clinicians' ability to predict PK and PD alterations within this complex clinical context is fundamental to ensure further optimal and, sometimes, individualized therapeutic plans that balance clinical outcomes with the minimum drug adverse events.

ECMO antimicrobial drugs anticoagulant drugs sedative drugs

1. Introduction

Drug pharmacokinetics (PK) and pharmacodynamics (PD) are subject to many factors, such as patient physiology and drugs' different physiochemical properties, including protein binding, hydrophilicity and molecular weight, among others. Alterations in drug PK are, in fact, the result of the influence of these properties on its clearance (CL) and volume of distribution (Vd). Patients' physiology-related alterations occur more frequently in critically ill patients where developed organ insufficiency or failure alter drug elimination rates. A decrease in hepatic perfusion or function can culminate into an induced increase in some drugs' toxicity. Hydrophilic drugs are mainly affected by both kidney function and blood flow reductions. Moreover, extracorporeal mechanical support (ECMS) has shown additional drug alterations in the same patients, such as an increased Vd in addition to either an increase or a decrease in drug CL [1].

ECMS is a technology used to temporarily replace cardiopulmonary function, including extracorporeal mechanical oxygenation (ECMO), a canonical example [2][3]. ECMO is largely being implemented worldwide as an essential lifesaving technique in many life-threatening situations, such as severe lung damage caused by an infection or cardiogenic shock. The use of ECMO has reached a maximum with the emerging COVID-19 pandemic, and according to the report of the 3rd annual meeting of the Chinese Society of Extracorporeal Support (CSECLS 2019), more than 435 ECMO centers exist worldwide with 13,394 cases treated by ECMO in 2018 [4]. Estimations from the Extracorporeal Life Support Organization (ELSO) report show that the survival rate using ECMO ranges between 58.7% and 73.2% for respiratory support and between 42.7% and 52.6% for circulatory support in a five-year period [5].

The ECMO equipment, mainly formed by a membrane oxygenator and the drive pump, is primarily designed to resolve hypoxemia and restore blood perfusion while the cardiopulmonary system is recovering or during heart–lung transplantation. In an ECMO setting, the pump functions similarly to the heart and drives the blood to flow along the tubes leading out of and flowing into the human body. On the other hand, the oxygenator or “artificial lung” replaces the lung function by ensuring gas exchange as well as regulating temperature [6]. Depending on the indications, ECMO connection to patients with cardiopulmonary failure follows at least two modalities, venous-to-arterial ECMO (VA) and venous-to-venous ECMO (VV) [7].

2. ECMO Modalities

2.1. VA-ECMO

VA-ECMO is mainly used as a quick and effective life-sustaining ECMS for patients with cardiogenic shock secondary to myocardial infarction or fulminant myocarditis while waiting for recovery or as a bridge to heart transplant [8][9].

2.2. VV-ECMO

The use of VV-ECMO generally implies draining the blood from a central vein, e.g., a femoral vein, and then injecting it back into a central vein, e.g., an internal jugular vein, as the most frequent modality [10]. VV-ECMO provides extracorporeal oxygen supply via the oxygenator, leading to improved oxygenated blood supply to the heart and organs with a minimal pulmonary workload. VV-ECMO is largely used in intensive care unit (ICU) patients with reversible lung dysfunction and respiratory failure [11] and can also be indicated in some cases as a bridge to lung transplant [12].

2.3. General Effects of ECMO on Drugs

Despite its use as life support for patients with cardiopulmonary failure, ECMO represents a long-duration invasive respiratory and circulatory assisting system. Thus, drug monitoring for ECMO patients is challenging over time, as ECMO affects drugs’ PK at different levels and by different mechanisms [1][13]. Priming solutions that are used to initiate the ECMO support, such as plasma, normal saline, and/or albumin affect mainly hydrophilic drugs’ Vd, leading to significantly decreased drug plasma concentrations and potentially therapy failure. Priming solutions contribute to an increased volume that causes plasma protein dilution, affecting drug–protein binding and leading to supra-therapeutic free drug levels, which may lead to toxicity if the usual drug doses are used, especially with narrow therapeutic index drugs. Drug sequestration is another way that ECMO can cause drug PK alterations due to some properties of ECMO circuits. Sequestration particularly happens within the membrane oxygenator and the circuit tubing due to their large surfaces and affects lipophilic drugs, leading to their adsorption and loss over time [1][14][15].

Antimicrobials, anticoagulants, sedatives, and analgesics are commonly used drugs during ECMO support. Several studies have shown altered PK profiles for these drugs in patients on ECMO [16][17], rendering their effective dosing a challenge to clinicians. However, PK data are still lacking with limited guidance.

2.4. Alterations in Drug PK Profiles during ECMO

2.4.1. Circuit and Drug Factors

Drug Sequestration

Drug sequestration is variable based on both the ECMO setting and the drug in question [1]. Lipophilic and highly protein-bound drugs are more prone to sequestration in ECMO circuits; hence, the relationship between the administered dose and the anticipated blood concentration can be established based on assumptions related to the drug's physicochemical properties. Generally, these features are reported by the drug's octanol–water partition coefficient or logP. Moreover, molecular size and drug ionization could theoretically play a role in drug sequestrations [18][19][20].

Although oxygenators provide a large surface area for drug sequestration, research data showed that their contribution is minimal compared to conduit tubing effects [20][21][22]. The drug's logP determines the drug's lipophilicity; increased positive logP values indicate augmented lipophilicity, while negative values are proportionally related to decreased lipophilicity. Owing to their relatively higher solubility in the organic component of the ECMO circuit, lipophilic drugs have been constantly shown to be more prone to sequestration when compared with hydrophilic drugs. Additionally, drug sequestration comparisons based on varying degrees of protein binding within ECMO circuits demonstrated that drugs with higher protein binding are found to be considerably sequestrated despite similar lipophilicity [23].

Circuit Priming

Different drugs' PK can be affected by circuit priming. Related influencing factors are the type of priming fluid, pH, temperature, and added electrolytes. The exact phenomenon by which circuit priming may affect drug sequestration, leading to potential consequences such as therapeutic failure or toxicity, is yet to be studied [24], but it could be related to the increased effective circulating volume in ECMO patients following circuit priming.

Circuit Age

Circuit type and age can affect the degree of drug loss within the ECMO circuit [14][22][25]. New circuits have shown a higher sequestration effect on specific drugs, such as phenobarbital, vancomycin, gentamicin, and phenytoin, when compared to a used circuit [19]. Other drugs, such as morphine, also showed significantly decreased steady-state concentrations (from 68.2 to 11.6 ng/mL) within new circuits, suggesting that aged circuits could be saturated and lead to less drug sequestration. Thus, in such a situation, the newly used ECMO circuit may require higher drug doses and closer monitoring [19].

Patient Factors

Low plasma protein levels, commonly seen in critically ill patients, lead to an increased free fraction of protein-bound drugs, resulting in altered drug CL, Vd, and enhanced drug effects. Moreover, critically ill patients are more prone to significant modifications in serum pH, which may also lead to paralleled dissociation of protein-binding drugs [23]. Vd is also one of the most affected PK parameters in critically ill patients with volume status imbalances and fluid shifts. Furthermore, underlying diseases, associated organ dysfunction, and systemic inflammation would also contribute to multiple PK changes, such as an increase in Vd and a decrease in drug CL [26][27][28]. Other features, such as obesity, may also play a critical role in PK changes. In fact, increased adipose tissue provides sites for the sequestration of lipophilic drugs. Moreover, drugs with lower Vd would have significant alterations in their Vd because of increased patients' fluid volume compared to drugs with larger Vd, which tend to be lipophilic. Another feature is multi-organ failure, specifically acute kidney injury, a common situation in patients utilizing ECMO, leading to reduced drug CL [29][30].

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