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Direct and continuous dosing of propofol can saturate Ex vivo ECMO circuit to improve propofol recovery

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Abstract – Background: Extracorporeal membrane oxygenation (ECMO) is a cardiopulmonary bypass device that provides life-saving complete respiratory and cardiac support in patients with cardiopulmonary failure. The majority of drugs prescribed to patients on ECMO lack a dosing strategy optimized for ECMO patients. Several studies demonstrated that dosing is different in this population because the ECMO circuit components can adsorb drugs and affect drug exposure substantially. Saturation of ECMO circuit components by drug disposition has been posited but has not been proven. In this study, we have attempted to determine if propofol adsorption is saturable in Ex vivo ECMO circuits. Methods: We injected Ex vivo ECMO circuits with propofol, a drug that is highly adsorbed to the ECMO circuit components. Propofol was injected as a bolus dose (50 μg/mL) and a continuous infusion dose (6 mg/h) to investigate the saturation of the ECMO circuit. Results: After the bolus dose, only 27% of propofol was recovered after 30 minutes which is as expected. However, >80% propofol was recovered after the infusion dose which persisted even when the infusion dose was discontinued. Conclusion: Our results suggest that if ECMO circuits are dosed directly with propofol, drug adsorption can be eliminated as a cause for altered drug exposure.

Keywords: ECMO, Propofol, Saturation, Dosing.

Overview

Extracorporeal membrane oxygenator (ECMO) is a cardiopulmonary bypass device that provides complete respiratory and cardiac support in patients with severe cardiopulmonary failure and is a lifesaving technology for critically ill patients. Critically ill patients on ECMO are prescribed multiple drugs but the dosing for most drugs is unknown. Dosing for this population is different due to 1) direct adsorption of drugs by the circuit, 2) clearance by the circuits (e.g., hemofiltration), and 3) critical illness physiology which affects drug absorption, distribution, metabolism, and elimination [1, 2]. Altered drug pharmacokinetics (PK) can result in suboptimal dosing and place patients at risk for subtherapeutic exposure and toxicity [3]. Adsorption of the drug to circuit components is primarily driven by hydrophobic and electrostatic interactions [4]. Studies have suggested that this process might be saturable but this has never been proven [5, 6]. Propofol is a commonly used sedative that is highly lipophilic (logP = 3.8) and protein-bound (98%) and is known to be adsorbed by the ECMO circuit. Prior studies have demonstrated that up to 70% of propofol was adsorbed within 30 minutes of administering a bolus dose to the Ex vivo ECMO circuit [7–9]. In this study, we repeated the single dose experiment and additionally gave a 2-hour infusion of propofol to determine if propofol adsorption was saturable in a pediatric Ex vivo ECMO circuit.

Description

ECMO circuits were assembled according to standard practice with a Quadrox iD oxygenator with biolene coating, Rotaflow R32 pump with biolene coating and custom perfusion tubing. Circuits were set up in a closed loop with an IV bag representing the “patient”. Circuits were primed with human-packed red blood cells (330 mL), fresh frozen plasma...
where tubing of the ECMO circuit is made of poly(vinyl chloride) (PVC) and the oxygenators are made of poly(methyl pentene) (PMP), which are both hydrophobic. By saturating the circuit, propofol will then be available for its primary purpose: sedation. However, it is difficult to directly translate ex vivo results to a clinical setting because the experiments only quantify the drug-circuit interactions and it is unknown if propofol administered directly to the patient would achieve the same saturation. To address this, we have developed an approach that translates ex vivo results into dosing recommendations. One limitation of this study is that we set up the circuit as we would for a pediatric patient and hence results may not translate directly to an adult circuit. However, although we used a pre-configured pediatric tubing set and set the flow rate to 1 L/min, our ex vivo circuit had an adult oxygenator (common practice in pediatric ECMO centers). Because adsorption is dependent in part on (150 mL), plasmalyte (100 mL), heparin (250 units), sodium bicarbonate (3.5 mEq), tromethamine (2 g), calcium gluconate (325 mg) and albumin (6.25 g) and adjusted to maintain physiological conditions. The flow was set to 1 L/min to mimic flows for a 10 kg child. For the control, 30 mL of primed blood was drawn from the ECMO circuit and transferred to a tube, and maintained at 37 °C in a water bath. Both the ECMO circuit and control were dosed with propofol at t = 0 to achieve a target concentration of 50 μg/mL (for clinical relevance). Samples (1 mL) were collected at different time points (1, 5, 15, 30, 60, 120, 180, and 240 mins). After the 240-minute sample, the ECMO circuit was dosed with a continuous infusion of 6 mg/h representing the low end of dosing for a 10 kg child. The infusion was discontinued after 2 hours. Samples were collected at the following time points: 15, 30, 60, and 120 min after start of infusion and 1, 5, 15, 30, 60, 120, and 240 mins after discontinuing infusion. Collected blood samples were centrifuged immediately (@3000 rpm, 4 °C) and plasma samples were stored at −80 °C until ready for further analysis. The samples were then analyzed for propofol concentration using HPLC, and then converted to propofol remaining (propofol recovery) using the following equation:

\[
\text{Recovery} \% = \frac{C_t}{C_i} \times 100,
\]

where \(C_t\) is the concentration at time \(t\) and \(C_i\) is the concentration at time = 1 min for the bolus dose and \(C_i\) is the concentration at time = 15 mins for the infusion dose.

Results

The percentage recovery of propofol was then plotted against time (Figure 1). All circuits and controls were run in triplicate.

For the bolus dose, the control demonstrated a very high recovery of propofol (above 80% at all time points) whereas in the ECMO circuit, a rapid decrease in propofol recovery was observed after the bolus dose, with a recovery of only 27% at 30 mins (Figure 1 and Table 1). However, when administered as a continuous infusion, propofol recovery was >80% during the infusion and that high level of recovery persisted even after the infusion was discontinued.

Discussion

Our results following a bolus dose of propofol are consistent with previous investigations on recovery of propofol [7–9]. As noted in those studies, approximately 70% of propofol is adsorbed on the ECMO circuit components after 30 mins of a bolus dose. Our results were consistent with previous studies as we observed 72% propofol to be absorbed on the ECMO circuit components after 30 mins of a bolus dose. Our results following a continuous infusion suggest that propofol adsorption is saturable when administered through the circuit. The saturation of the circuit can occur due to the hydrophobic interactions between the hydrophobic drug propofol and the hydrophobic material of the ECMO circuit components. The tubing of the ECMO circuit is made of poly(vinyl chloride) (PVC) and the oxygenators are made of poly(methyl pentene) (PMP), which are both hydrophobic. By saturating the circuit, propofol will then be available for its primary purpose: sedation of the patient. However, it is difficult to directly translate ex vivo results to a clinical setting because the experiments only quantify the drug-circuit interactions and it is unknown if propofol administered directly to the patient would achieve the same saturation. To address this, we have developed an approach that uses physiologically based pharmacokinetic modeling (PBPK) to translate ex vivo results into dosing recommendations. One limitation of this study is that we set up the circuit as we would for a pediatric patient and hence results may not translate directly to an adult circuit. However, although we used a pre-configured pediatric tubing set and set the flow rate to 1 L/min, our ex vivo circuit had an adult oxygenator (common practice in pediatric ECMO centers). Because adsorption is dependent in part on
flow rate in an ex vivo circuit, in order to translate this to an adult ECMO circuit, higher doses of propofol would be required. Another potential limitation is that propofol rapidly distributes out of the plasma when administered to a patient, and it is unknown if those low concentrations in the plasma would be sufficient to saturate the circuit. There are some concerns that administering a lipophilic drug directly to an ECMO circuit can increase clotting and impair oxygenator function [10]. Another unknown is the possibility of the circuit acting as a reservoir and leading to the leaching of the drug back into circulation and causing toxicity [5]. Consequently, additional ex vivo and in vivo work is required before dosing propofol directly to the circuit can be routinely recommended.

Conclusion

In summary, this is the first study to definitively show that adsorption by the ECMO circuit is saturable after an infusion dose is administered. Furthermore, these results demonstrate the potential of removing adsorption as a source of altered drug exposure by saturating the circuit. Additional work is needed to determine the optimal dose and if direct administration to the circuit impacts circuit function.

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Conflict of interest

The authors declare that they have no conflict of interest.

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Data availability

The data are available from the corresponding author upon reasonable request.

Author contributions

Nitish Khurana: Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Validation, Writing – original draft; Till Süenner: Investigation, Methodology; Carina Imburgia: Investigation, Methodology; Venkata Yellepeddi: Conceptualization, Funding Acquisition, Methodology, Writing – review and editing; Hamidreza Ghandehari: Conceptualization, Funding Acquisition, Methodology, Writing – review and editing, Supervision; Kevin M. Watt: Conceptualization, Funding Acquisition, Methodology, Writing – review and editing, Supervision.

References