Sedative and Analgesic Drug Sequestration in Modern ECMO Circuits-Pilot data
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Introduction
Sedation and analgesia while on ECMO is vital for patient safety and comfort, yet drug pharmacokinetics change markedly with initiation of ECMO therapy. ECMO circuits have been altered to alter patients’ pharmacokinetics with an increased volume of distribution, decreased clearance and increased drug adsorption onto the ECMO circuit itself. Previous studies have shown that lipophilic drugs such as fentanyl are rapidly and thoroughly adsorbed by ECMO circuits, sequestering as much as 100% of fentanyl at 24 hours after single bolus injection. These studies were performed using older ECMO circuits that included silicone membrane oxygenators (MO), and non-coated polyvinylchloride (PVC) tubing. In clinical practice today, PVC tubing is coated with agents such as heparin or other proteins, and silicone is replaced with polymethylpentene (PMP) in the MO to decrease size and increase efficiency.

This study seeks to better characterize drug adsorption of Fentanyl, Morphine, Midazolam and Dexmedetomidine in modern neonatal ECMO circuits utilizing a polymethylpentene (PMP) membrane oxygenator (MO) with protein bounded polyvinylchloride (PVC) tubing.

Methods
Closed-loop ex-vivo ECMO circuits are prepared using P.h.i.s.i.o. coated PVC neonatal tubing (Sorin Group USA, Inc.) and a Quadrox-D Pediatric polymethylpentane MO (Maquet Cardiopulmonary AG). A closed-loop system is created allowing continuous flow of the priming fluid around the circuit with Revolution Centrifugal Pump (Sorin Group USA, Inc). The priming solution consists of blood products, heparin, albumin, sodium bicarbonate and calcium gluconate. One drug is injected per circuit to avoid competition for the theoretical patient weight of 5 kg. Drug samples are drawn at times 0, 2, 5, 15, 30, 60, and 120 minutes and then at 4, 12, 24, 36 and 48 hours. Samples are analyzed in duplicate using liquid chromatography with mass spectrometry (LC/MS).

Results
Two ECMO circuits per drug were utilized for fentanyl (2ug/kg), morphine (0.1mg/kg), midazolam (0.1mg/kg) and dexmedetomidine (1ug/kg). 69% of dexmedetomidine, 56% of fentanyl, 27% of midazolam, and 100% of the Morphine remains in the ECMO after 48hours.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Total volume (ml)</th>
<th>Dose (μg)</th>
<th>Theoretical conc.</th>
<th>Actual conc.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>600</td>
<td>10</td>
<td>16.67 ng/ml</td>
<td>9.46 ng/ml</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>600</td>
<td>500</td>
<td>0.833 μg/ml</td>
<td>0.856 μg/ml</td>
</tr>
<tr>
<td>Morphine</td>
<td>600</td>
<td>5</td>
<td>8.33 ng/ml</td>
<td>5.74 ng/ml</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>500</td>
<td>500</td>
<td>0.833 μg/ml</td>
<td>0.227 μg/ml</td>
</tr>
</tbody>
</table>

Possible sequestration of fentanyl, midazolam and dexmedetomidine in ECMO circuits may limit drug delivery to patients. Improved understanding of the pharmacokinetics of these drugs in ex-vivo may help pediatric anesthesiologists and intensivists provide a better sedative and analgesic strategy for patients on ECMO.

References

Conclusion

![Graphs of drug concentrations over time](attachment:drug_concentrations.png)