Introduction

- Extracorporeal membrane oxygenation (ECMO) temporarily supports respiratory and cardiovascular function in critically ill neonates.
- Midazolam (MDZ) i.v. is used to prevent distress and cannula dislodgement.
- Major metabolites 1-hydroxymidazolam (OHM) and its glucuronide (HMG) contribute to overall sedation.
- ECMO is associated with PK changes due to disrupted organ function, adsorption and edema.

Aim

To describe ECMO-induced PK changes of MDZ, OHM and HMG, and to select a suitable dose regimen through simulations.

Methods

- We included 20 patients on venoarterial ECMO, with a median postnatal age (range) of 0.79 (0.17-5.8) days, and a body weight of 3.0 (2.7-3.9) kg at onset of ECMO. ECMO duration was 124 (70-275) h.
- Plasma concentrations were measured during midazolam infusion (100-300 μg/kg/h). In total, 293 samples were analysed.
- Nonlinear mixed-effects modeling (NONMEM 6.2) was used with FOCE to model MDZ, OHM and HMG PK.
- Clearances and volumes of distribution were allometrically scaled.

Results

- A 2-compartment model for MDZ and 1-compartment for OHM and HMG adequately described the data, with allometric scaling of CL and V parameters (Fig. 1 and 2).
- $V_{MDZ}$ increased asymptotically during the first hours of ECMO, with a half life of 1.85 h.
- Median $CL_{MDZ}$ and $CL_{OHM}$ increased with $t_{EC}$ and PNA resp., whereas $CL_{HMG}$ remained constant (Fig. 3).
- Unexplained interpatient variability on $CL_{MDZ}$, $CL_{OHM}$, $CL_{HMG}$, $V_{MDZ}$ and $V_{HMG}$ was 87% - 129%.
- Concomitant infusion of vasoressive catecholamines increased $CL_{HMG}$ by 23% (Fig. 3C).

Conclusion

- Continuous MDZ infusion of 300 μg/kg/h for 6 h, and 150 μg/kg/h thereafter, provides adequate plasma concentrations (400 ng/mL) to sedate ECMO-patients (Fig. 4).
- The MDZ infusion rate will have to be increased (+33%) after 5 days, to compensate for increased MDZ and OHM clearance.

Table 1. Representative parameter estimates for an ECMO-treated neonate (WT = 3kg, PNA = 0.8 days at cannulation)

<table>
<thead>
<tr>
<th></th>
<th>MDZ</th>
<th>OHM</th>
<th>HMG</th>
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<tbody>
<tr>
<td>CL (mL/kg/min)</td>
<td>0.56</td>
<td>2.58</td>
<td>7.58</td>
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<tr>
<td>V (L/kg)</td>
<td>1.43</td>
<td>3.58</td>
<td>7.60</td>
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<tr>
<td>$t_{EC}$ (hr)</td>
<td>15.7</td>
<td>4.5</td>
<td>3.4</td>
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Fig 3. Allometrically scaled clearance estimates vs time on ECMO ($t_{EC}$) for MDZ (a), OHM (b) and HMG (c). Curves are individual posthoc estimates, with a median curve (interrupted)

Fig 4. Simulated plasma concentrations of MDZ, OHM and HMG using the proposed dose regimen. The total level of MDZ equivalents (interrupted curve) is based on a relative potency of 80% (OHM) and 8% (HMG) compared to MDZ.