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# Population PK of Midazolam and Metabolites during Venoarterial ECMO in Neonates

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## 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.

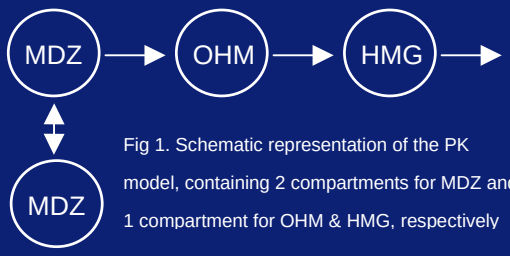


Fig 1. Schematic representation of the PK model, containing 2 compartments for MDZ and 1 compartment for OHM & HMG, respectively

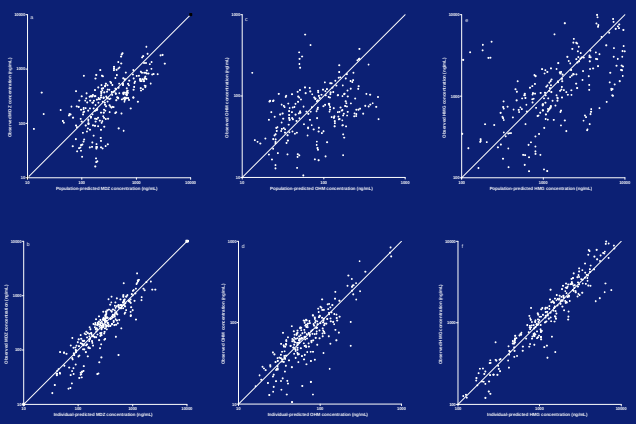

Fig 2. Goodness-of-fit plots for the final model, with PRED vs DV (a,c,e) and IPRED vs DV (b,d,f) for MDZ, OHM and HMG

## 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.

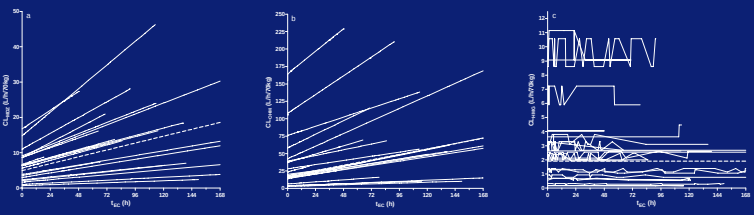

Fig 3. Allometrically scaled clearance estimates vs time on ECMO ($t_{EC}$) for MDZ (a), OHM (b) and HMG (c). Curves are individual posthoc estimates, with a median curve (interrupted)

## 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 vasopressive catecholamines increased $CL_{HMG}$ by 23% (Fig. 3C).

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

| | MDZ | | | | | OHM | | | | | HMG |
|---|---|---|---|---|---|---|---|---|---|---|---|
| $t_{EC}$ (h) | 0 | 24 | 120 | 240 | 336 | 0 | 24 | 120 | 240 | 336 | - |
| CL (mL/kg/min) | 2.58 | 3.58 | 7.60 | 12.6 | 16.6 | 9.25 | 13.2 | 29.1 | 49.0 | 64.9 | 0.99 |
| V (L/kg) | 1.43 | 4.86 | 4.86 | 4.86 | 4.86 | 3.41 | 3.41 | 3.41 | 3.41 | 3.41 | 0.40 |
| $t_{\frac{1}{2}}$ (hr) | 6.4 | 15.7 | 7.4 | 4.5 | 3.4 | 4.3 | 3.0 | 1.4 | 0.8 | 0.6 | 4.7 |

## 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.

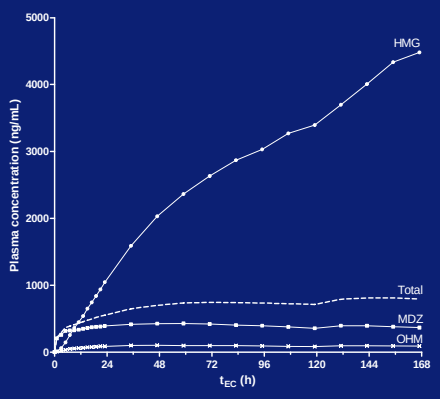


Fig 4. Simulated plasma concentrations of MDZ, OHM and HMG using the proposed dose regimen. The total level of MDZ equivalents (interrupted curve) is based on a relative potency of 80 % (OHM) and 6 % (HMG) compared to MDZ



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