Investigating the hypothesis of lysosomal trapping of 1'-hydroxymidazolam using PBPK modelling

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Background

- One-hydroxy-midazolam (1'-OH-MDZ), the primary CYP3A4-mediated metabolite of midazolam (MDZ), requires accurate PK prediction for proper assessment of CYP3A4 activity and understanding overall drug drug interactions (DDI). [1]
- Previous PBPK modelling of MDZ accurately predicted 1'-OH-MDZ exposure but overpredicted C_{max} concentrations, suggesting intracellular retention mechanisms. [2]
- The physicochemical properties of 1'-OH-MDZ (logP ≈ 2, pKa > 6) make it prone to pH-dependent lysosomal trapping. [3,4]

Objectives

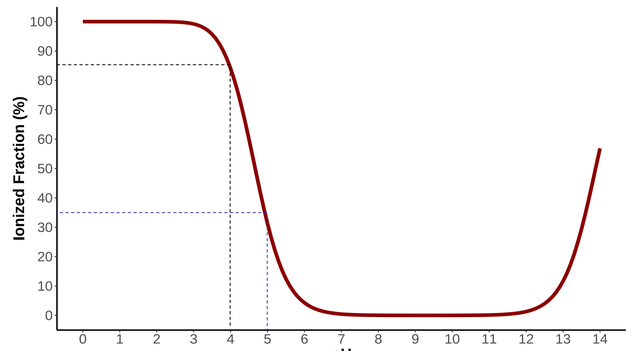

Figure 1: Total Ionised fraction of 1'-OH-MDZ as a function of pH

- This study test the lysosomal trapping hypothesis of 1'-OH-MDZ by refining an existing PBPK model after IV midazolam administration of 1mg in health volunteers (N=17) in MoBi.

Methods

- We enhanced the MDZ PBPK model by integrating lysosomal compartments (2% of intracellular volume) in liver, spleen, kidney, and lungs at pH 4.51.
- Organ-specific partition coefficients were precisely calculated using MATLAB.
- Model performance was evaluated by comparing predicted and observed plasma PK profiles graphically, and by calculating C_{max} and AUC_{0-10}.

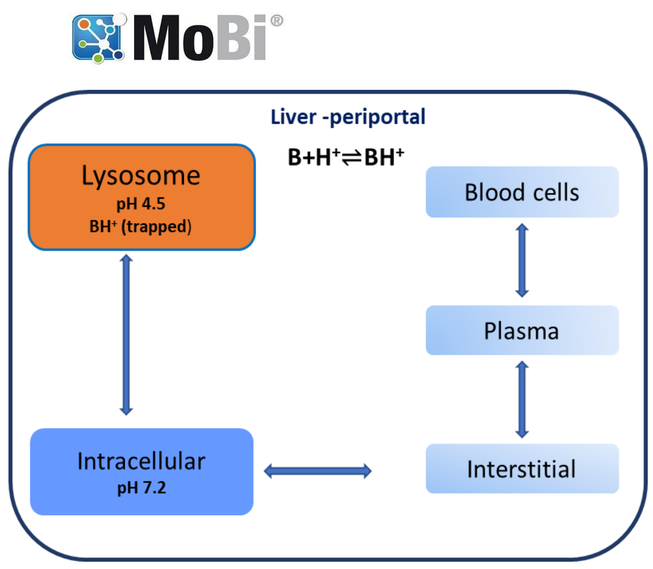

Figure 2 : Mechanistic representation of lysosomal trapping incorporated in the MoBi PBPK model (Liver - Periportal compartment).

Results

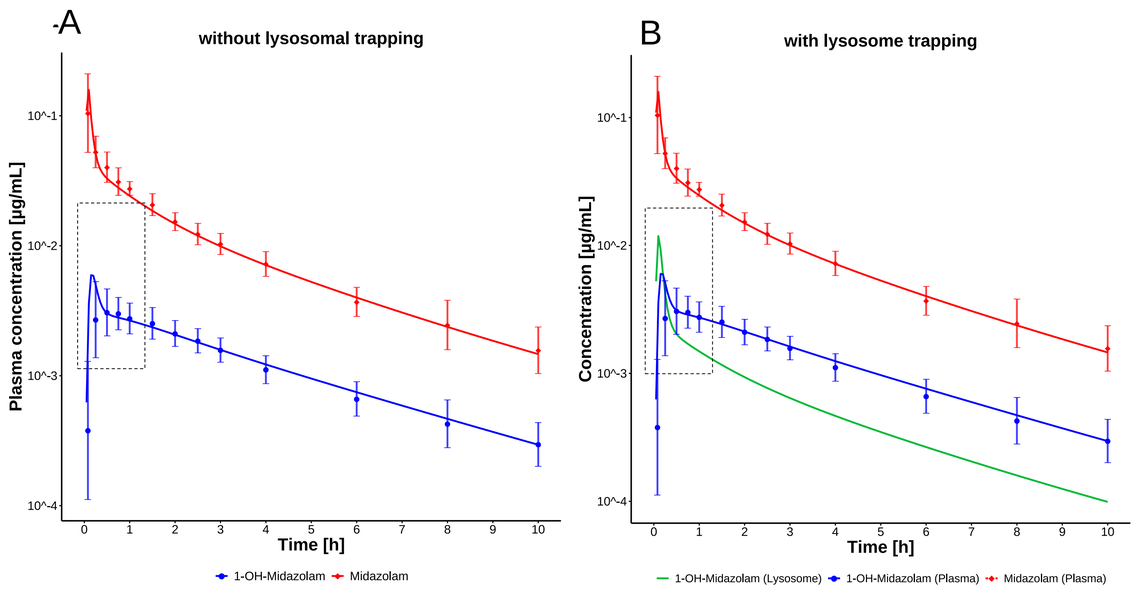

Figure 3. PBPK model prediction of Midazolam and 1'-OH-MDZ exposure comparing model without lysosomal trapping (A) vs *a priori* model with lysosomal trapping showing plasma and lysosomal compartments (B) after single i.v infusion. Circles: mean observed plasma concentration; Solid lines: mean predicted concentration; Red: MDZ; Blue: 1'-OH-MDZ ; Green: lysosomal concentrations; over 10-hour time course.

Table 1. Pharmacokinetic parameters of 1'-OH-MDZ : Model Comparison

Parameter [units]	Without lysosome	With lysosome
C_{max} [10^{-3} µg/mL]	5.94	6.00
AUC_{0-10} [µg·h·mL^{-1}]	0.76	0.78

Results cont

Table 2. Parameters of 1'-OH-MDZ lysosomal trapping PBPK model

Parameter [units]	Value
Volume of lysosome(V_L) [L]	0.03
pH of lysosome	4.50
Partition coefficient (water/lysosome) (Kp)	0.72
K_cell_lys [Lmin^{-1}]	1.00

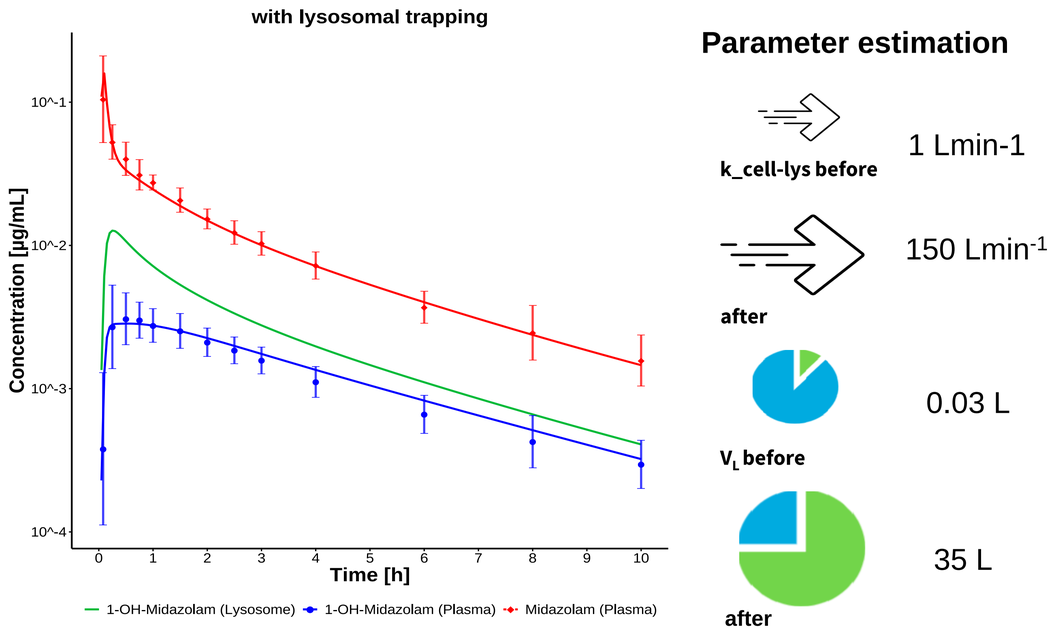

Figure 4. PBPK model prediction of MDZ and 1'-OH-MDZ exposure using optimised model with lysosomal trapping after single i.v infusion. Circles: observed plasma concentration-time profiles; Solid lines: predicted concentration-time profiles; Red: MDZ plasma; Blue: 1'-OH-MDZ plasma; Green: 1'-OH-MDZ lysosomal concentrations

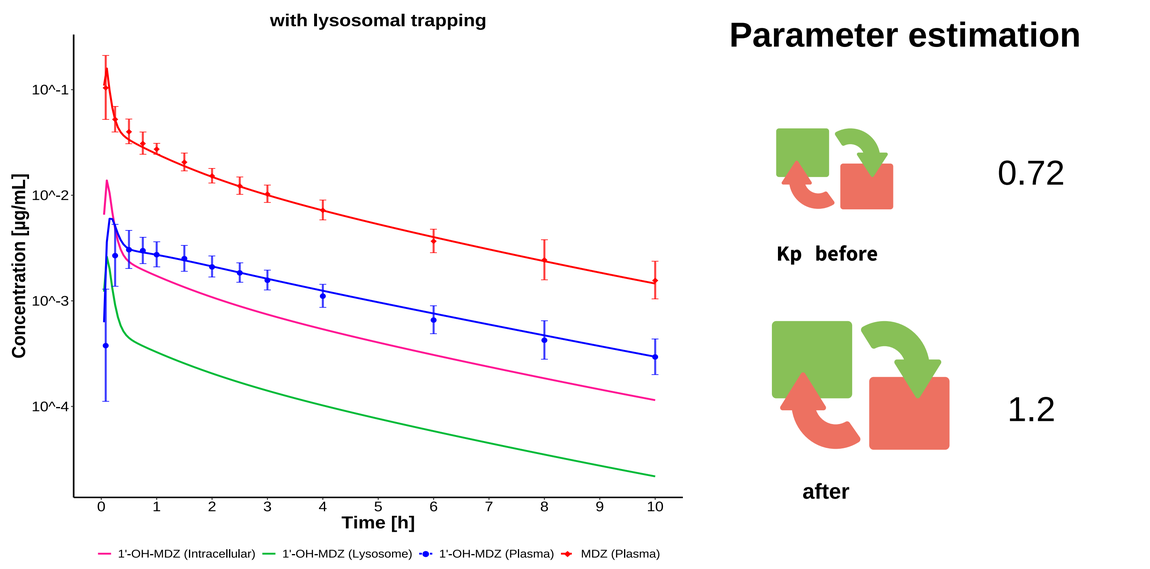

Figure 5. Compartmental distribution of MDZ and 1'-OH-MDZ following i.v administration with lysosomal trapping model. MDZ (red line) and 1'-OH-MDZ (blue line) in plasma compared to observed data (points with error bars), alongside predicted 1'-OH-MDZ concentrations in hepatic intracellular (pink line) and lysosomal (green line) compartments.

Discussion and Conclusions

- Lysosomal trapping was identified as a background process that did not significantly impact the overall plasma concentration-time profile of 1'-OH-MDZ before parameter estimation step.
- Parameter estimation improved 1'-OH-MDZ C_{max} predictions when lysosomal volume and intracellular-to-lysosome flow were increased to non-physiological levels (up to 35 L and 150-fold flow). Thus, lysosomal trapping appears to have limited influence on plasma concentrations under physiologically realistic conditions. [4]
- Estimating the partition coefficient did not affect the C_{max} or overall plasma trajectory of 1'-OH-MDZ but rather the amount in the lysosome and the cellular spaces.

- We were able to test the lysosomal trapping effect of 1'-OH-MDZ by incorporating the lysosomal compartment into the coupled whole-body PBPK model which did not improve much the model fit to 1'-OH-MDZ clinical data.
- The refined PBPK model provide a mechanistic framework for predicting lysosomal accumulation of basic drugs and metabolites. Further exploration of this mechanism could enhance model-based predictions, particularly for compounds where lysosomal accumulation may play a role in their disposition.
- For the purpose of DDI studies the current MDZ and metabolite model is sufficient for quantifying metabolite to parent ratio

References

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2. PAGE 29 (2021) Abstr 9842 [www.page-meeting.org/?abstract=9842]
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4. M.V.Schmitt *et al* DrugMetab.Dispos.49:53–61(2021).

Abbreviations 1'-OH-MDZ:1-hydroxymidazolam; AUC_{0-10} : Area Under Curve from 0 to 10 hours; C_{max} : Maximum Concentration; CYP3A4: Cytochrome P450 3A4; Fu: Fraction Unbound; IV: Intravenous; K_cell_lys: Cellular Lysosomal Uptake Rate Constant; Log P: Logarithm of Partition Coefficient; MATLAB: Matrix Laboratory; MDZ: Midazolam; PBPK: Physiologically-Based Pharmacokinetic; pH: Potential of Hydrogen; PK: Pharmacokinetics; vs: Versus

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