A generic PBPK model for predicting the impact of inflammation on midazolam pharmacokinetics

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Introduction

Systemic inflammation is known to impact drugs pharmacokinetics (PK) :

- IL-6 binding to its membrane receptor activates different signaling pathways modifying activity of nuclear receptors involved in drug-metabolizing enzymes (DME) and drug-transporters synthesis [1].
- In vitro tests have studied the impact of some cytokines exposure on hepatic, intestinal and blood-brain barrier cell lines. They reveal alterations of expression levels and activities of DMEs, drug-transporters and plasma proteins [1, 2, 3].
- Clinical studies have also highlighted significant differences of PK profiles between patients with high and low systemic inflammation level [4].

→ These modifications could have clinical consequences and require **dosing rate adaptations**.

Aims

The aim of this work was to build a physiologically-based PK (PBPK) model **to predict the impact of inflammation** on drug PK. Since **CYP3A4**, one of the major DME, is strongly impacted by inflammation, midazolam was chosen as a probe for this study.

Data & Methods

In a previous study, we conducted RNA sequencing and activity tests on intestine and BBB cell lines to select which DME and ABC transporters are the most impacted by inflammation.

Model building

Midazolam PBPK model was built using PK-sim 7.4 and its library.
The inflammation model was calibrated using midazolam PK profiles after continuous infusion at four levels of CRP (10, 32, 100 and 300 mg/L) in a population of 83 critically ill children [5].

The relationship between CRP concentrations and CYP3A4 metabolic clearance was processed with Mobi 7.4.
Metabolic CYP3A4 activity was described as a saturable process following Michaelis-Menten kinetics.

Model validation

The model was externally validated using visual predictive check (VPC).
The data of 12 rheumatoid arthritis patients taking 0.03mg/kg midazolam (oral route), before and after administration of sirukumab (an anti-IL-6 monoclonal antibody) [6] were compared to simulations for N = 1000 patients performed with PK-sim for different CRP concentrations (0.5 and 25.3 mg/L).

Results

A] Building inflammation-metabolism correlation using simulations from critically hill children (N=83) [5]

Severity of inflammation was related to CYP3A4 metabolic activity by including a factor, kcrp, on midazolam-metabolite formation rate equation :

$$\frac{dN}{dt} = kcrp * \frac{kcat*[MDZ]}{Km+[MDZ]}, \ kcat = Vmax/[CYP3A4]$$

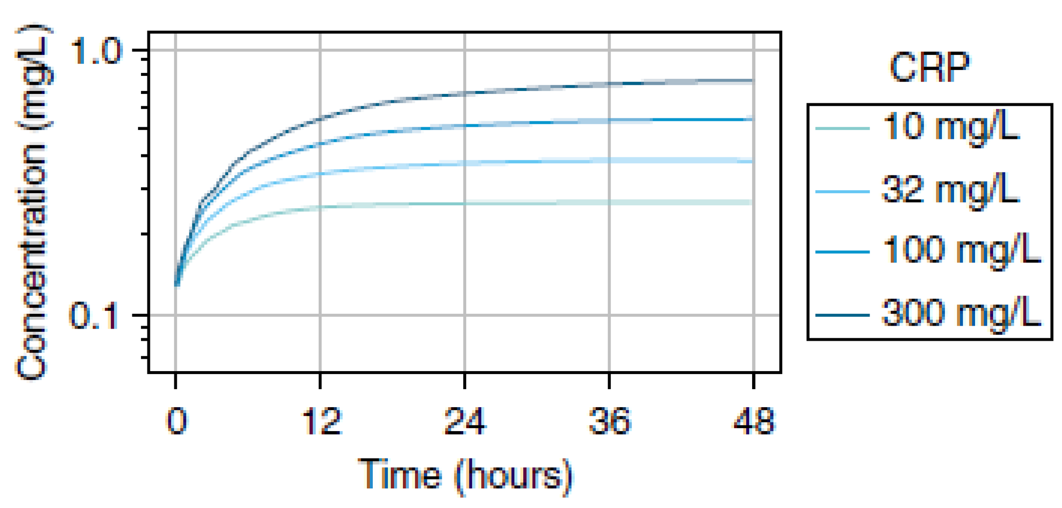
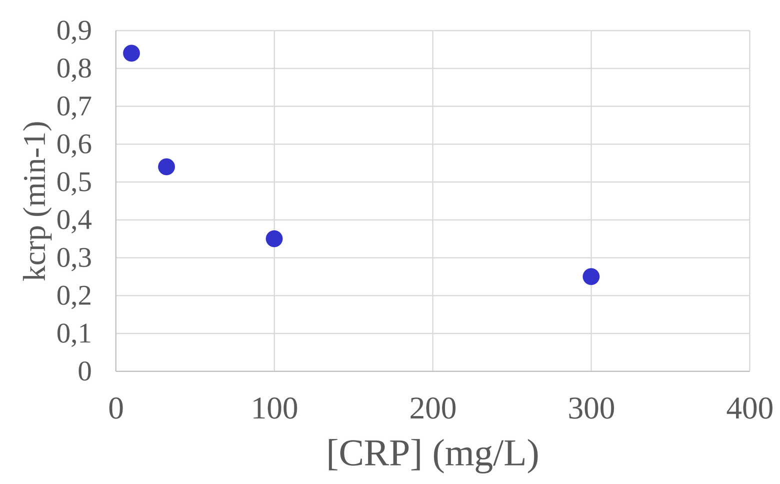


Fig. 1 Midazolam simulations for different CRP levels (10, 32, 100 and 300 mg/L) (Vet et al. 2016)

Estimation of kcrp for each midazolam PK profile :



$$kcrp = 0.2 + 0.8 * e^{-\frac{ln2}{25}*[CRP]}$$

B] Model validation using PK data from rhumatoid arthritis patients (N=12) before (CRP = 25.3 mg/L) and after (CRP = 0.5 mg/L) tocilizumab treatment [6]

CRP = 0.5 mg/L

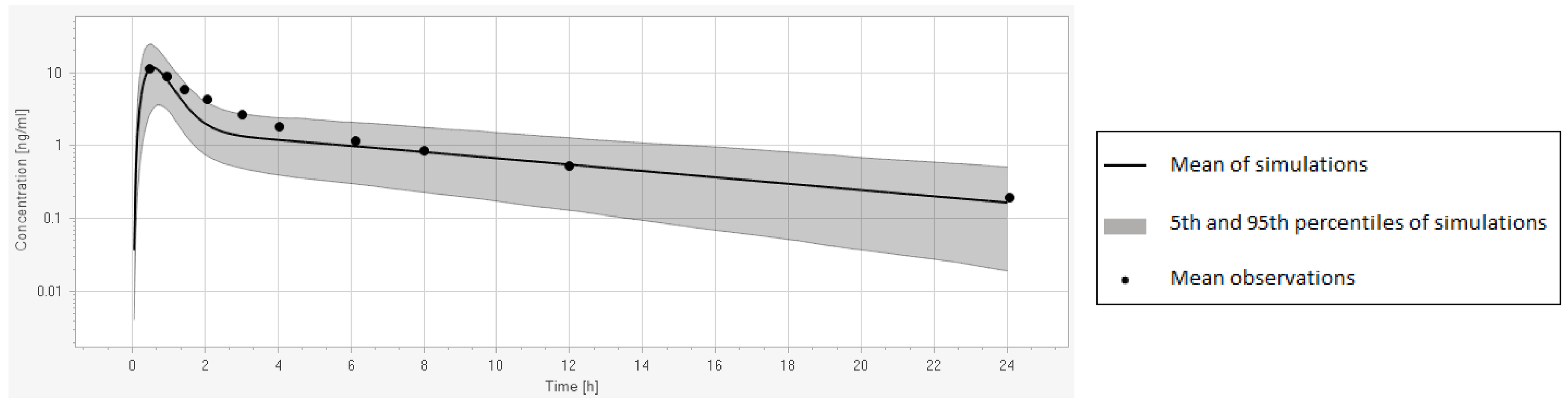


Fig. 2 Visual Predictive Check (VPC) based on N=1000 simulations with CRP = 0.5 mg/L

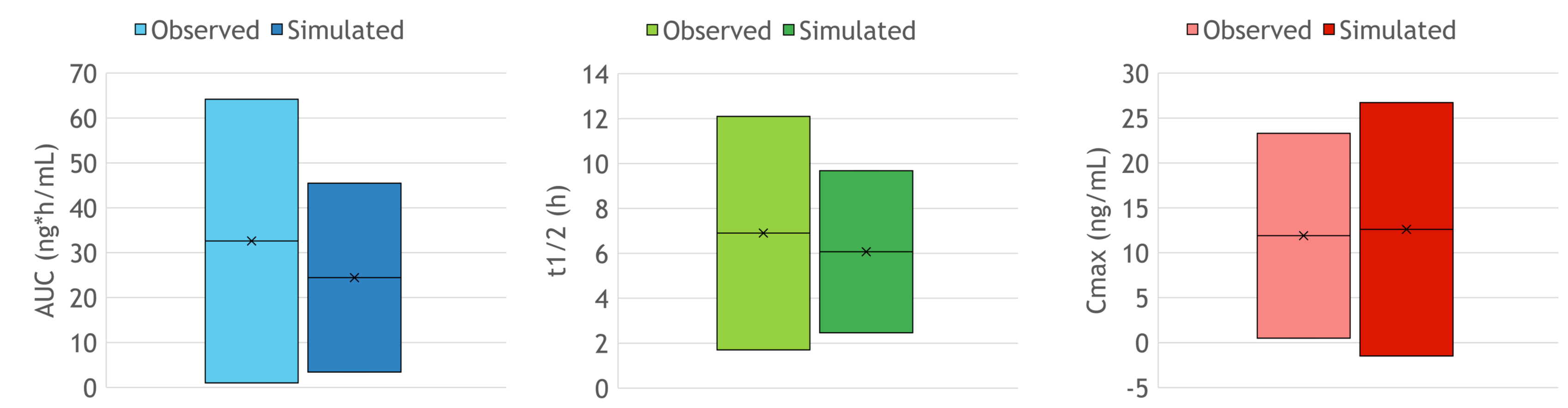


Fig. 3 AUC_{inf}, $t_{1/2}$ and C_{max} (Mean ± 2*SD) from observations (N=12) and simulations (N=1000) with CRP = 0.5 mg/L

CRP = 25.3 mg/L

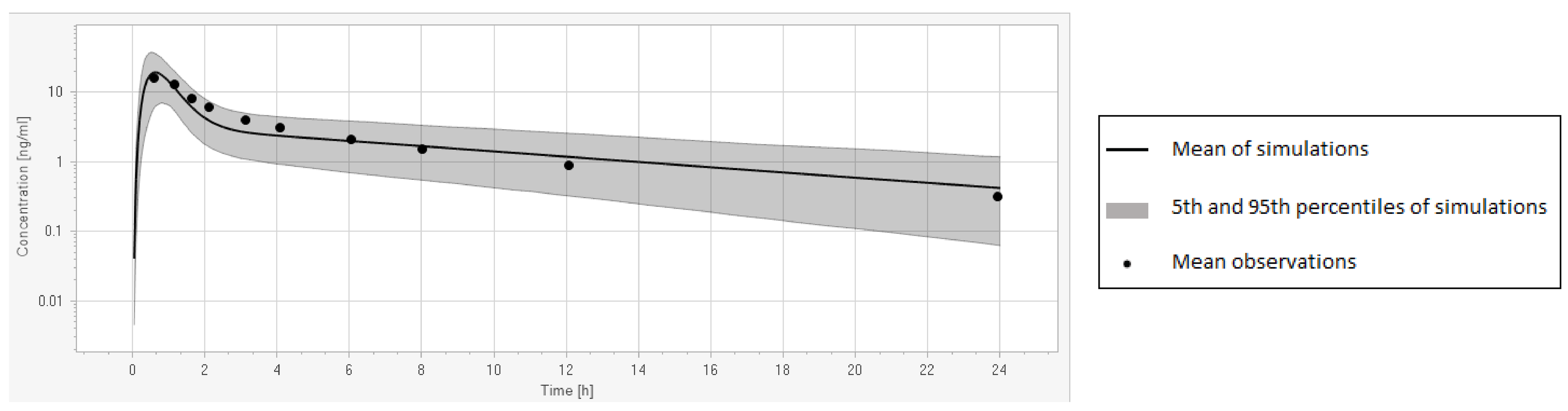


Fig. 4 Visual Predictive Check (VPC) based on N=1000 simulations with CRP = 25.3 mg/L

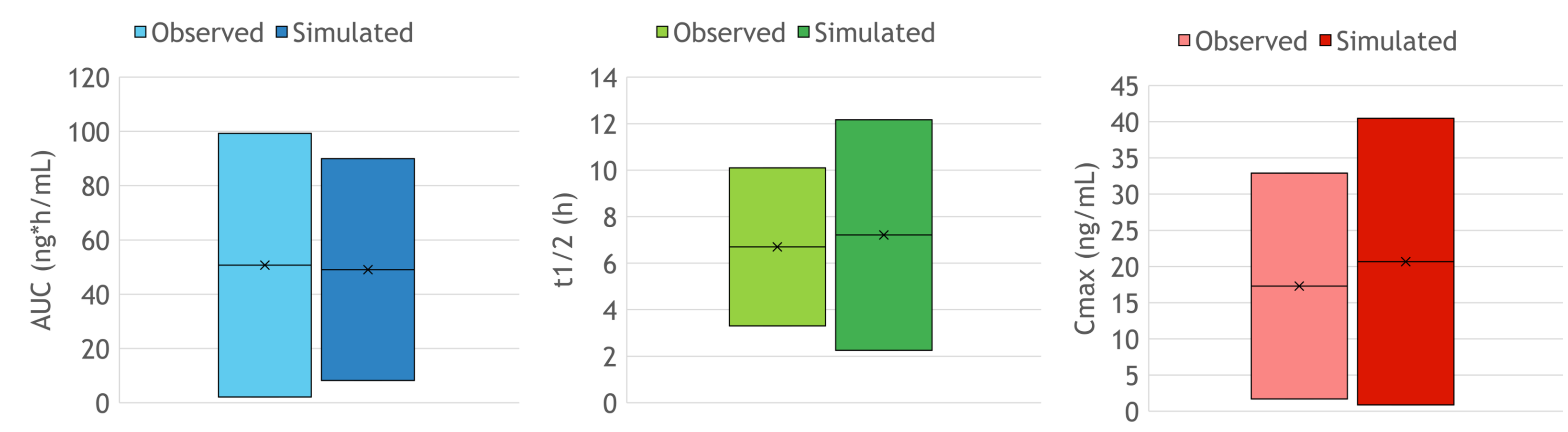


Fig. 5 AUC_{inf}, $t_{1/2}$ and C_{max} (Mean ± 2*SD) from observations (N=12) and simulations (N=1000) with CRP = 25.3 mg/L

Conclusion

- Midazolam PK could be predicted depending on the level of CRP.
- This model allows to adapt dosing rate of CYP3A4 substrates and to avoid toxicities in case of high inflammatory response.
- This approach will be extended to other substrates of DMEs impacted by inflammatory response and to drugs with high protein binding in plasma.
- Effect of inflammation on drug-drug interactions will also be studied.

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