Evaluation of Clinical DDI Potential of Methotrexate Using PBPK Modeling

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Background

Low-dose and high-dose methotrexate (MTX) are used to treat rheumatoid arthritis and malignancies, respectively. Given the narrow therapeutic index of MTX, it is necessary to assess the potential of candidate drugs to perpetrate a drug–drug interaction (DDI) with MTX during development.

Methods

Table 1. Input parameter values used in MTX model

Parameter	Value	Method/Reference
Molecular weight (g/mol)	454.44	
log P	-1.85	https://www.drugbank.ca/drugs/DB00563
Compound type	Diprotic Acid	
pKa	4.7, 3.36	Poe, 1977
B/P	0.68	Salzer *et al.,* 2012
fu	0.5	Herman *et al.,* 1989
Main plasma binding protein	Human serum albumin	Herman *et al.,* 1989
fa	0.9	Hospira, 2011
ka (1/h)	4.25	Stewart *et al.,* 1990
Lag time (h)	0.6	
Distribution	Full PBPK Model	
V_{SS} (L/kg)	0.39	Predicted - Method 2
Elimination		
CL_{int} (HLM) (µL/min/mg)protein)	0.24	Retrograde calculation– assign 5% of CL_{IV}
CL_{int} (Bile) (µL/min/10^6 cells)	0.164	Retrograde calculation– assign 10% of CL_{IV}
Mechanistic Kidney Model		
$CL_{PD,basal}$ and $CL_{PD,apical}$ (mL/min/million proximal tubular cells)	2.57E-06	Xia *et al.,* 2007
Uptake Transporter	SLC22A8 (OAT3)	
$CL_{int,T}$ (µL/min/million cells)	0.39	Kurata *et al.,* 2014
REF	16	Based on manual fitting to the clinical data (Hubner *et al.,* 1997)
Efflux Transporter	ABCC4 (MRP4)	
$CL_{int,T}$ (µL/min/million cells)	2.75	Nozaki *et al.,* 2007
REF	2.27	Fitted to the observed urine profiles (Haagsma *et al.,* 1996). Assumed basolateral uptake clearance is equal to the apical efflux

- A mechanistic kidney model for MTX was developed within Simcyp v17.1. Low-dose and high-dose simulations were performed using Sim-Rheumatoid Arthritis population and the Sim-Cancer population, respectively.
- In vitro uptake data [1,2] describing the OAT3-mediated uptake into the kidney cells and MRP2/4 mediated efflux into the urine were incorporated. The REF values for OAT3 and for MRPs were optimized using plasma (OAT3) and urine (MRPs) profiles for MTX, respectively.
- The contribution of OAT3 to MTX disposition was verified using the clinical MTX-probenecid DDI data [3]. The lowest reported OAT3 IC_{50} value of 0.76 µM [4] was incorporated into the default SV-Probenecid model.

Results

Figure 1. Simulated and observed (symbols) plasma concentration-time profile of methotrexate following the administration of an IV bolus dose of 15 mg in rheumatoid arthritis patients (A) or 200 mg/m² in cancer patients (B) or an oral dose of 15 mg in rheumatoid arthritis patients (C and D). Observed data was extracted from Seideman *et al.,* 1995, Stewart *et al.,* 1990 and Aherne *et al.,* 1978.

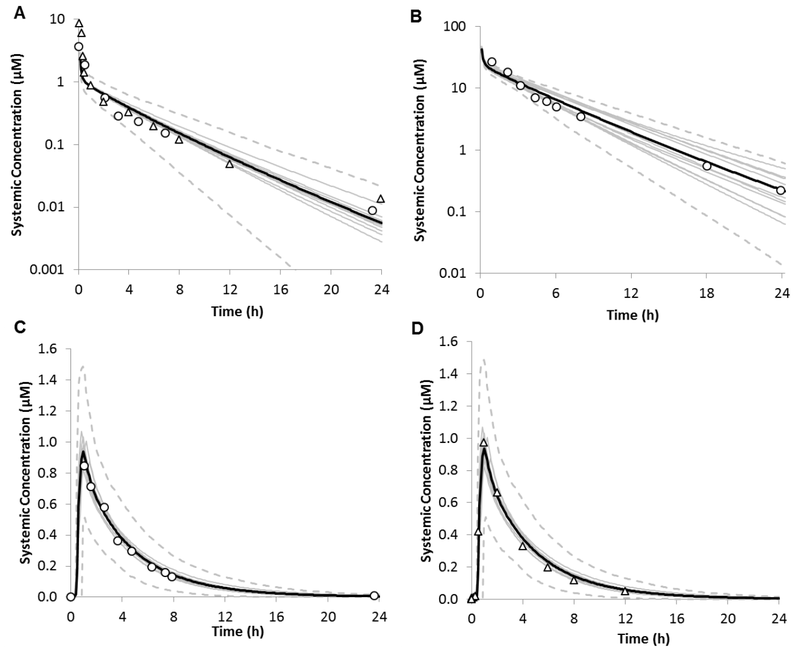

Table 2. Observed and predicted mean CL_{IV} and CL_R of MTX(200 mg/m² IV bolus) following co-administration of probenecid (500 mg p.o. given as two doses)

	CL_{IV} (L/h)		CL_R (L/h)	
	Obs	Pred	Obs	Pred
Control	6.5	6.71	6.2	5.75
Inhibited	4.1	3.95	2.7	2.65

- The developed MTX model recovered the observed pharmacokinetic data after intravenous 15-200 mg/m² and 7.5-15 mg oral dosing of MTX.
- To verify the contribution of OAT3, the MTX model was applied to evaluate probenecid DDI: The predicted MTX (200 mg/m² IV bolus) AUC ratio with the co-administration of probenecid (500 mg p.o. two doses 6 hrs apart) was 1.70-fold *versus* the reported ratio of 1.57-fold.
- To gauge the uncertainty around OAT3 IC_{50}, the probenecid model was independently applied to predict the DDI potential of another OAT3 substrate, pemetrexed [5].
- The predicted pemetrexed DDI using a literature pemetrexed model [5] is 3.4-fold, consistent with *in vitro* evidence showing pemetrexed to be a better OAT3 substrate drug than MTX.

Conclusions

- The developed MTX model can be applied for prospective prediction of MTX DDI with another perpetrator drug. Literature reports[5] and the current analysis support the use of the lowest in vitro OAT3 Ki value for assessing OAT3-mediated DDIs.

References

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5. Posada et al., *Drug Metab Dispos.* 2015 Mar;43(3):325-34

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