A Physiologically-Based Pharmacokinetic (PBPK) Model of Cyclosporine: Method Standardization and Improved Understanding of Conformational Effects

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Introduction

- Cyclosporine can take on a hydrophilic and hydrophobic conformation
- Simulations only account for the hydrophilic conformation, but in vivo, cyclosporine is dynamic
- The goal of the study is to use GastroPlus™ to simulate the IV and oral pharmacokinetics of cyclosporine and understand the conformational changes in vivo
- Beyond cyclosporine, another goal is to develop a reliable systematic approach that can be applied to any other drug

Methods

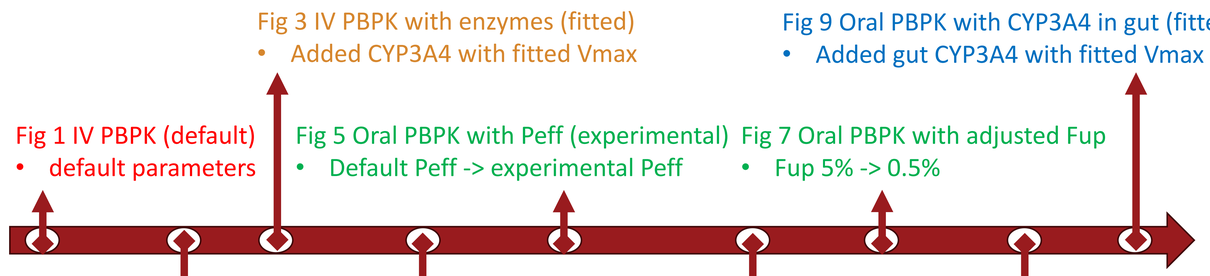
- Literature data for cyclosporine were collected for physiochemical parameters, metabolizing enzymes, and transporters that affect cyclosporine pharmacokinetics
- Experimental parameters were introduced into GastroPlus™ based on decision tree approach to determine appropriate changes
- The model was built in four main steps:

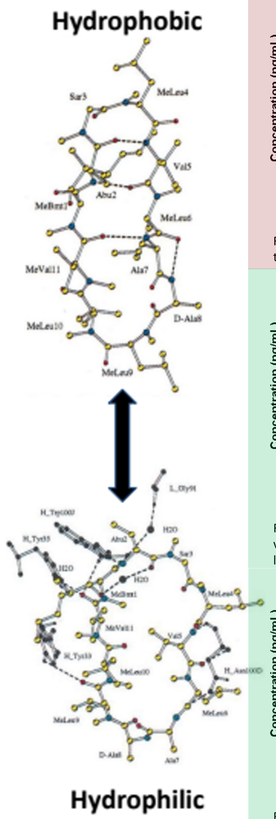
1) Fit the distribution for the IV administration while including non-mechanistic clearance
2) Fit mechanistic clearance (enzyme kinetics) for IV administration
3) Fit absorption in oral administration
4) Evaluate gut and liver metabolism

Model Development

- The IV model was fitted by adjusting the Fup and RBP from 22.3% and 0.73 (predicted) to 5% and 0.17 (experimental)
- CYP3A4 Vmax in the liver was adjusted from 9.16×10^{-5} mg/s/mg-enzyme (experimental) to 1.374×10^{-2} mg/s/mg-enzyme (fitted) (units shown as in GastroPlus™)
- Peff was adjusted to 12.049×10^{-4} cm/s (experimental); this large increase from 0.8×10^{-4} cm/s (default) is justified since GastroPlus™ treats cyclosporine as more hydrophilic
- Fup should be the same in the IV and oral model; however, since cyclosporine is dynamic, the change from 5% (IV) to 0.5% (oral) may reflect different conformations of cyclosporine

Model Development





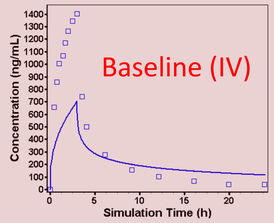


Fig 1: IV cyclosporine plasma concentration vs. time using default parameters in GastroPlus™

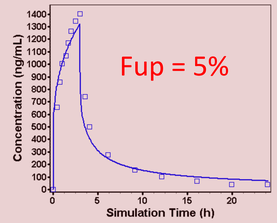


Fig 2: IV cyclosporine plasma concentration vs. time using experimental value of Fup and RBP

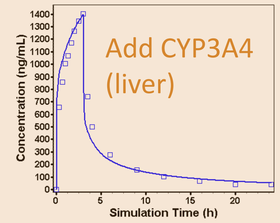


Fig 3: IV cyclosporine plasma concentration vs. time with the addition of CYP3A4 in the liver

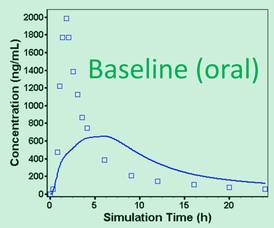


Fig 4: Oral cyclosporine plasma concentration vs. time using same Fup, RBP, CYP3A4, and logP as IV model

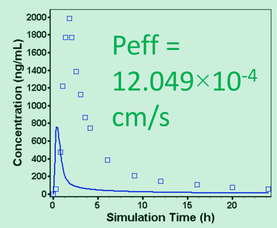


Fig 5: Oral cyclosporine plasma concentration vs. time using experimental value of Peff

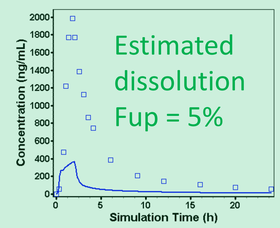


Fig 6: Oral cyclosporine plasma concentration vs. time with the addition of a dissolution

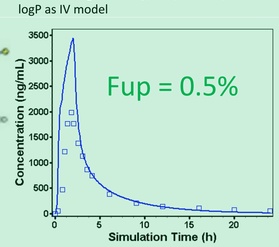


Fig 7: Oral cyclosporine plasma concentration vs. time changed Fup from 5% to 0.5%

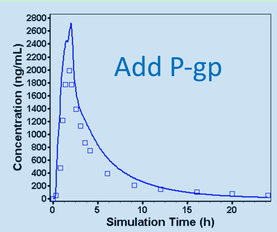


Fig 8: Oral cyclosporine plasma concentration vs. time with the addition of P-gp

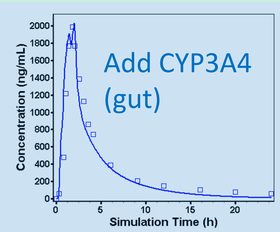


Fig 9: Oral cyclosporine plasma concentration vs. time with the addition of CYP3A4 in the gut

Results

IV		
Figure	Cmax (ng/ml)	AUC (ng*hr/ml)
1	703	5393
2	1322	6535
3	1399	6442
Exp	1404	6573

Oral			
Figure	Tmax (hr)	Cmax (ng/ml)	AUC (ng*hr/ml)
4	6.16	651.6	8394.4
5	0.4	760.27	1275
6	2	369.2	1256.6
7	2	3451.2	11000
8	2	2727.9	10900
9	2	2035.2	7082.1
Exp	1.79	1986.7	8101.1

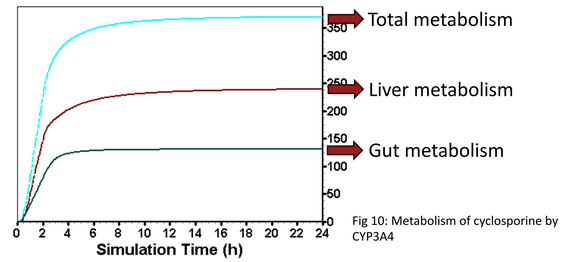


Fig 10: Metabolism of cyclosporine by CYP3A4

Discussion

- The developed cyclosporine model is largely based on experimental data
- A systematic approach was used for development of the model
- A key difference between the IV and oral models was the much lower **Fup** in the oral model
- A lower Fup indicates that a more hydrophobic conformer is present
- In oral delivery, the cyclosporine has to be in the hydrophobic form to be absorbed
- In IV delivery, we anticipate that most will still be in the hydrophobic form, but there will be some of the hydrophilic form will be present
- Therefore, the requirement of a change in Fup from IV to oral model may be a consequence of the different conformations of cyclosporine that are present in vivo

References

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