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

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Background

Cyclosporine is a cyclic peptide indicated for prophylaxis of organ rejection in kidney, liver, and heart allogeneic transplants. Despite its widespread use in clinical practice, the pharmacokinetics of the drug are not fully understood. Simulation software, like GastroPlus™, can be used to build and evaluate pharmacokinetic models. However, this is challenging for cyclosporine because the drug has two conformations that are hydrophilic and hydrophobic, respectively, while the software can only model one of these conformations.

Methods

Literature data for cyclosporine were collected for physicochemical parameters, metabolizing enzymes, and transporters that affect cyclosporine pharmacokinetics. These data were used to build a physiologically-based pharmacokinetics (PBPK) model in GastroPlus™. Experimental parameters were introduced into GastroPlus™ based on a decision tree approach to determine appropriate changes at each step in model development. The fit of the simulated model to observed plasma concentration vs. time data for IV and PO administration was used to judge the success of each step. The model was built in four main steps: (1) fit the distribution for IV administration while including non-mechanistic clearance; (2) fit mechanistic clearance (enzyme kinetics) for IV administration; (3) fit absorption in PO administration; and (4) evaluate gut and liver metabolism.

Results

In step (1), the IV model was fitted by adjusting the fraction unbound (Fup) and red blood cell plasma ratio (RBP) from 22.3% and 0.73 (predicted values) to 5% and 0.17 (experimental). In step (2), CYP3A4 was added with Vmax adjusted from 9.16×10^{-5} mg/s (experimental, units as shown in GastroPlus) to 1.374×10^{-2} mg/s (fitted) and Km was maintained at 2.878 mg/L (experimental). In step (3), a PO model was built using experimental data for permeability and P-glycoprotein kinetics, adjusted CYP3A4 kinetics in the gut wall, an estimated dissolution curve, and Fup of 0.5%. In step (4), the model was shown to be consistent with experimental information showing that close to 50% of cyclosporine is metabolized in the gut wall.

Conclusion

The developed cyclosporine model is largely based on experimental data. A key difference between the IV and PO models was the much lower Fup in the oral model. We believe that this is due to the presence of a greater amount of the hydrophobic conformer immediately after absorption, compared to that after infusion. Some adjustments of kinetic parameters were required, particularly for CYP3A4 Vmax, and these changes are currently being examined for other drugs to improve understanding of parameter adjustments required to build accurate PBPK models.