The influence of dissolution, PMAT influx, and MATE efflux rates on paracellular absorption of metformin using a mechanistic oral absorption / PBPK model

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PURPOSE

A physiologically based absorption and distribution model was developed for metformin to facilitate our understanding of the influence of transporters and dissolution rate on oral absorption.

RESULTS

A single set of transporter and values implemented in the GastroPlus ACAT model were found to accurately fit all of the human clinical literature data. It was also observed that the rate and extent of absorption was relatively insensitive to the lumenal release rate of metformin from immediate release formulations. For these formulations, the simulations showed that the relative rates of influx and efflux changed the regional location of paracellular absorption and modified the Tm, but Cmax and AUMC were less sensitive. Simulated absorption for classical extended release formulations resulted in much lower exposure due to the smaller paracellular pore size in the lower GI and colon. However, the simulations for gastric retentive Glucophage XR formulations were bioequivalent with IR formulations.

METHODS

A mechanistic oral absorption ACAT / PBPK model for metformin was developed using GastroPlus™ (Simulations Plus, Inc., Lancaster CA). The model incorporated PMAT influx and MATE efflux transporters on the apical membrane of the intestinal lumen, along with paracellular permeability as the only route of absorption into the portal vein. Systemic clearance was modeled by using permeability-limited liver and kidney tissues with the following transporters: OCT1 (basolateral gut and liver influx), OCT2 (basolateral kidney influx), and MATE2K (apical kidney efflux). Transporter Km values were taken directly from in vitro literature studies and Vmax values were optimized to fit the observed clinical data. The model was validated by comparing the simulation results to literature results (Tucker 1981, Pentikainen 1979, and Balan 2001) for intravenous and oral administration assuming solution, IR, ER, and XR formulations of metformin administered to human subjects under fasted and fed conditions. The influence of dissolution rate on the rate and extent of metformin absorption was tested by using a variety of intestinal lumen metformin release rates using Weibull function profiles.

GUT MODEL SCHEMATIC

CONCLUSIONS

The mechanistic oral absorption-PBPK model developed for this study is one of the first to include the influence of intestinal apical transporters and paracellular absorption of metformin (see also Kakhi and Lukacova, 2015 AAPS Annual meeting presentation). The model is suitable to help generic formulation development and to test for virtual bioequivalence. The model can also be used for simulations of transporter-mediated drug-drug interactions.

REFERENCES

2. Almukainzi M. J. Diabet. Metab. 5:3 (2014)