Incorporation of an electrochemical driving force for the renal transport of metformin by OCT in a physiologically-based pharmacokinetic model of the interaction between metformin and cimetidine.

Poster No. M1018

howard.burt@certara.com

Howard J Burt[1], Sibylle Neuhoff[1], Lisa Almond[1], Matthew D Harwood, Masoud Jamei[1], Amin Rostami-Hodjegan[1&2], Geoffrey T Tucker[3] and Karen Rowland-Yeo[1]

[1]Simcyp (a Certara Company), Sheffield, UK. [2]Manchester Pharmacy School, Faculty of Medical and Human Sciences, University of Manchester, Manchester, UK.

[3]Medicine and Biomedical Sciences (emeritus), University of Sheffield, Sheffield, UK.

Purpose

Metformin is the first line treatment for type II diabetes. About half of an oral dose is absorbed, of which 80% is cleared unchanged by the kidneys[1,2]. Uptake of metformin into the kidney tubule by OCT2 and efflux into the tubular fluid by MATE's 1 and 2-K is indicated by *in vitro* studies, as is uptake into the liver by OCT1[3]. Cimetidine increases the plasma AUC of metformin by 1.5–fold[4,5]. It is an inhibitor of OCT's 1 and 2 and MATE's 1 and 2-K with K_i values of 120, 124, 3.8 and 6.9 µM, respectively in HEK293 cells[3]. The aim of this study was to recover the *in vivo* interaction using a mechanistic kidney model (Mech KiM) nested within the physiologically-based pharmacokinetic (PBPK) model in the Simcyp Simulator® (v.14) (Figure 1).

Methods

Base PBPK models - Full-PBPK models for metformin and cimetidine were developed within the Simcyp Simulator (v.14)[6]. *In vitro* data obtained using transfected HEK293 cells were incorporated in a permeability-limited liver model (PerL) and Mech KiM to describe transport of metformin by OCT1[3] and OCT2 and MATEs 1 and 2-K[3], respectively, and in Mech KiM to describe transport of cimetidine by OCT2[7], OAT3[7,8], MATE1[9,10] and MATE2-K[9]. A relative activity factor (RAF) for HEK293 cells of 3 was used to convert intrinsic transport clearances from µl/min/mg protein to µl/min/million proximal tubule cells or hepatocytes. OCT transport was described by first-order kinetics using intrinsic clearance (CL_{int}) inputs. Passive renal permeability clearances were scaled from PAMPA[11] and human jejunal[12] permeability data for metformin and cimetidine, respectively, based on the combined nephron tubule surface area of a pair of healthy kidneys. A passive permeability value for metformin uptake in liver was obtained from a study with cryopreserved hepatocytes[13].

Incorporation of 'electrogenic' OCT transport of metformin – A model in which the rate of OCT-mediated uptake of metformin depends on its electrochemical gradient (Eq 1. and Eq 2.) was investigated as an alternative to the first-order kinetic description used in the base PBPK model.

$$rate\ of\ uptake = \Phi_{df} \cdot J_{OCT} \qquad \text{Eq 1.}$$

$$\Phi_{df} = \Phi_m - \frac{R \cdot T}{z \cdot F} \cdot ln\left(\frac{[S]_{outside,u}}{[S]_{inside,u}}\right) \qquad \text{Eq 2.}$$

Where the *rate of uptake* is in units of pmol.min^{-1}, J_{OCT} is the rate (pmol.min^{-1}.volt^{-1}) of OCT1 or OCT2 -mediated transport, Φ_{df} is the electrochemical driving force (volts), Φ_m is the membrane potential (-0.035 and -0.06 volts in HEK293[14] and proximal tubule cells[15], respectively), R is the universal gas constant (8.314 Joules.Kelvin^{-1}.mol^{-1}), T is temperature (Kelvin), z is the valence of the ionic species (1 for metformin), F is Faraday's constant (96490 coulombs.mol^{-1}) and $[S]_{outside,u}$ and $[S]_{inside,u}$ are the unbound concentrations of metformin outside and inside the cell, respectively.

Estimates of J_{OCT} were first obtained by fitting *in vitro* uptake data for metformin generated in OCT2[16] and OCT1[17] transfected HEK293 cells using a two-compartment model. These estimates were then applied in a metformin PBPK model with the rate of uptake by OCT1 in the liver and OCT2 in the kidney described by equations equivalent to Eq 1. and Eq 2. RAF values of 1.1, 2.3 and 1.0 for OCT1, OCT2 and MATEs, respectively were required to recover baseline plasma metformin concentrations.

With both models, the *in vivo* studies of the metformin – cimetidine interactions[4,5] were simulated based on 10 virtual trials (250[4] or 500[5] mg oral metformin daily, with and without coadministration of 400 mg oral cimetidine BID).

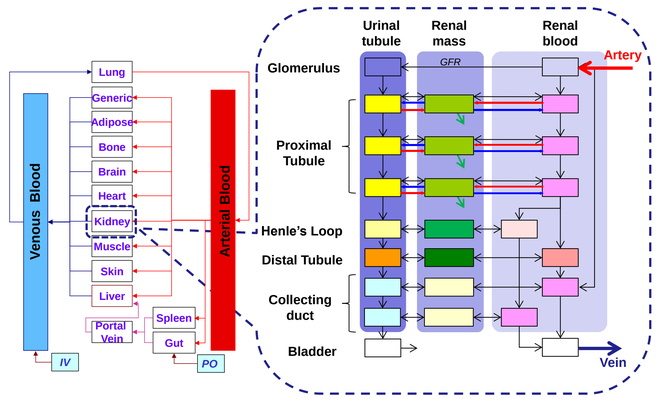

Figure 1 *- The mechanistic kidney model (Mech KiM) as a component of the full PBPK model within Simcyp v.14. Passive processes are represented by black arrows; metabolic, active uptake and efflux processes in the proximal tubule segments are represented by green, blue and red arrows, respectively.*

Results

Simulations with the base PBPK model predicted metformin plasma AUC to be insensitive to the inhibition of renal MATE1/2-K transport by cimetidine, despite a large increase in the metformin concentrations within proximal tubule cells (Fig 2A). A 1000-fold reduction in the cimetidine OCT2 K_i was required to recover the observed 1.5–fold AUC ratio (Fig. 2B).

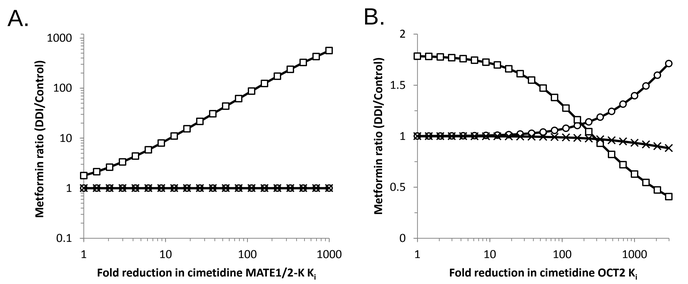

Figure 2 *- Sensitivity of ratios (DDI/Control) of metformin (O) plasma AUC, (□) AUC from proximal tubule cell segment 1 and (**X**) urinary recovery to cimetidine K_i values for (A) MATE1 and 2-K and (B) OCT2 based on the base PBPK model incorporating a conventional description of transport kinetics for both drugs.*

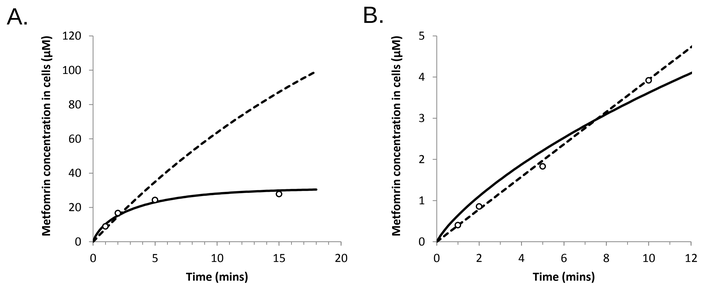

Figure 3 *- Comparison of the ability of a conventional model (dashed lines) and an electrogenic model (solid line) to describe experimental data (open circles) on the uptake of metformin by (A) hOCT2 transfected HEK293 cells[16] and (B) hOCT1 transfected HEK293 cells[17].*

The electrogenic model of OCT transport was able to recover data for metformin uptake into OCT2 transfected HEK293 cells (Fig 3A), although it did not describe uptake into OCT1 transfected HEK293 cells as well as the base model.

When the electrogenic model of metformin OCT uptake in kidney and liver was applied within the metformin PBPK model, inhibition of renal MATE transport by cimetidine influenced the activity of OCT2 such that a change in plasma metformin concentrations was predicted (Fig. 4).

However, 8 to 18-fold decreases in the cimetidine K_i's for OCTs and MATEs was still required to recover the observed 1.5 –fold AUC ratio. This degree of reduction is consistent with other attempts to recover transporter-mediated DDIs for solute carriers[18,19,20,21]. The reasons for this discrepancy are unclear but may be linked to the assumption of competitive inhibition and *in vitro* methodology.

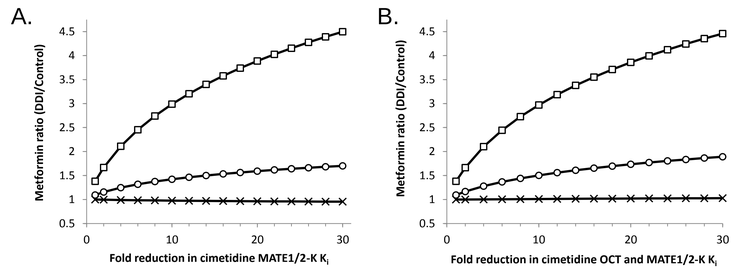

Figure 4- Sensitivity of ratios (DDI/Control) of metformin (O) plasma AUC, (□) proximal tubule cell segment 1 AUC and (**X**) urinary recovery to in cimetidine K_i for (A) MATE1 and 2-K and (B) OCT1 and 2 and MATE1 and 2-K, based on a PBPK model incorporating an electrochemical description of metformin OCT2 transport.

Conclusions

- When conventional kinetics for OCT2 transport were applied in a PBPK model for metformin, simulations were unable to recover an impact of inhibition of MATE1 and 2-K transport by cimetidine on plasma metformin concentrations.
- The alternative electrogenic model predicted an effect of MATE1 and 2-K inhibition by cimetidine on OCT2-mediated uptake and hence an increase in plasma metformin concentrations, reflecting a ~10-fold limit to intracellular drug accumulation.
- Decreases (8 to 18 fold) in the K_i values of cimetidine for OCTs and MATEs were still required to recover the observed extent of the DDI. An investigation into the causes of this is ongoing.

References

1. Tucker GT *et al.,* 1981, *Br J Clin Pharmacol* 12: 235
2. Sirtori CR *et al.,* 1978, *Clin Pharmacol Ther* 24: 683
3. Ito S *et al.,* 2012, *J Pharmacol Exp Ther* 340: 393
4. Somogyi A *et al.,* 1987, *Br J Clin Pharmacol* 2: 545
5. Wang Z-J *et al.,* 2008, Pharmacogenet Genom 18: 637
6. Burt HJ *et al.,* 2016, *Eur J Pharm Sci,* Early Online
7. Choi YH *et al.,* 2010, *Br J Pharmacol* 161: 815
8. Tahara H *et al.,* 2005, *J Pharmacol Exp Ther* 315: 337
9. Erdman AR *et al.,* 2006, *Am J Physiol Renal Physiol* 290: F905
10. Ohta KY *et al.,* 2009, *J Pharm Pharm Sci* 12: 388
11. Krishna R & Yu L (*Eds*), 2008, *Biopharmaceutics: Applications in Drug Development* Springer (New York) p119
12. Takamatsu N *et al.,* 2001, *Pharm Res* 18: 742
13. Sogame Y *et al.,* 2009, *Biopharm Drug Dispos* 30: 476
14. Veech *et al.*, 1995, *Integr Physiol Behav Sci* 30: 283
15. Pelis and Wright, 2011, *Compr Physiol* 1: 1795-1835
16. Kimura N *et al.,* 2005, *Pharm Res* 22: 255
17. Nies A *et al.*, 2011, *PLoS One* 6: e22163
18. Greupink R *et al.,* 2013, *Eur J Pharm Sci* 49: 819
19. Hsu V *et al.,* 2014, *Clin Pharmacokinet* 53: 283
20. Li R *et al.*, 2014, *Clin Pharmacokinet* 53: 659
21. Varma M *et al.*, 2012, *Pharm Res* 29: 2860