Introduction

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 kidney1,2. Uptake of metformin into the kidney tubule by OCT2 and efflux into the tubular fluid by MATE1 and 2 is indicated by in vitro studies, as is uptake into the liver by OCT1. Cimetidine increases the plasma AUC of metformin by 1.5 – 2 fold with no effect on its urinary recovery (Ae)3. This compound is an inhibitor of OCT1’s 1 and 2-K and MATE1’s 1 and 2-K (Ki values of 120, 124, 3.8 and 6.9 µM, respectively in HEK293 cells)4. Ki 11 µM for OCT2 in isolated proximal renal tubules5. The aim of this study was to recover the in vitro interaction using a mechanistic kidney model (Mech KiM) nested within the physiologically-based pharmacoKinetic (PBPK) model in the Simcyp Simulator® (v.12) (Figure 1).

Methods

Full-PBPK models for metformin and cimetidine were developed within the Simcyp Simulator® (v.12). Fractions absorbed and absorption rate constants were assigned from meta-analyses of published PK studies. Tissue to plasma concentration ratios (Kp) for both compounds were predicted using the method of Rodgers and Rowland6. For metformin, a permeability-limited liver (PerL) model was used.

Metabolism – A metabolic clearance of metformin was incorporated based on data generated in recombinant CYP3A47, and the metabolic clearance of cimetidine was set at 80% of total clearance based on meta-analyses of published PK studies.

Transport - In vitro data obtained using transfected HEK293 cells were incorporated into PerL and Mech KiM for transport of metformin by OCT1 and OCT2 and MATE1 and 2-K, respectively, and in Mech KiM for transport of cimetidine by OCT28, OAT39, MATE1 and MATE10. In the absence of relative activity/expression factors (RAF/REF) for HEK293, a scalar of 3 was used to convert intrinsic transport clearances from µl/min/mg protein to µl/min/million proximal tubule cells or hepatocytes. Renal passive permeability clearances were scaled from PAMPA10 and human jejunal11 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 hepatocytes12.

Trial design – Simulations were performed to evaluate the impact on metformin AUC and amount excrated unchanged in urine (Ae) of complete knockout of renal MATE1 and MATE2-K (Scenario 1) and complete knockout of renal OCT2 (Scenario 2).

The in vitro study of the metformin - cimetidine interaction was simulated for 10 virtual trials using the same study design (n = 7 healthy subjects aged 19-23 y) receiving 250mg oral metformin daily for 5 days, with and without coadministration of 400mg oral cimetidine BID.

Simulations were performed using:

- OCT2 and MATE1/2-K Ki values from HEK293 studies3,7 (Scenario 3)
- OCT2 Ki value from fresh proximal tubule cells3,7 (Scenario 4)
- OCT2 Ki obtained by sensitivity analysis (Scenario 5)
- OCT1 and OCT2 Ki values obtained by sensitivity analysis (Scenario 6)

Results

The outcomes of the six scenarios are illustrated in Figure 2.

- Complete knockout of MATE efflux had no effect on metformin AUC but decreased its Ae by 72% (Scenario 1).
- Complete knockout of OCT2 uptake increased metformin AUC by 2.3-fold and decreased Ae by 35% (Scenario 2).
- Application of the in vitro cimetidine Ki values for OCT2 and MATE1/2-K indicated negligible effects on the AUC and Ae of metformin (Scenarios 3 and 4, respectively).
- The observed increase in metformin when the cimetidine Ki for OCT2 was decreased from 11 µM to 0.5 µM, and this was associated with only a small (10%) decrease in Ae (Scenario 5). Figure 3 shows full plasma metformin profiles in the presence and absence of cimetidine.
- Equitopic inhibition of renal OCT2 and hepatic OCT1 by cimetidine (Ki 2µM) recovered the observed AUC ratio of metformin, with a small increase in its Ae (Scenario 6).

Conclusions

- Mech KiM in conjunction with in vitro data was used to evaluate the impact of OCT2 uptake versus MATE1/2-K efflux on the observed DDIs between cimetidine and metformin.
- An unaltered metformin AUC when there is complete knockout of MATE mediated efflux in the current model reflects the low passive transcellular permeability of the drug from the tubular cell back into plasma. In reality there may be return flux as OCT2 may change directionality at high intracellular substrate concentrations.
- Ki values for cimetidine measured in vitro could not recover the observed metformin AUC ratio; both the observed AUC and Ae data could only be recovered by sensitivity analysis of Ki values. This may reflect that the mechanism of transporter inhibition is more complex, possibly involving time-dependent effects requiring a pre-incubation step in in vitro study design.
- The small increase in metformin Ae when both hepatic OCT1 and renal OCT2 inhibition by cimetidine was simulated is consistent with a decreased hepatic availability for the metabolism of metformin.

References