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An assessment of the OCT2/MATE transporter mediated interaction between metformin and cimetidine using a mechanistic kidney model (Mech KiM)

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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 kidney[1,2]. Uptake of metformin into the kidney tubule by OCT2 and efflux into the tubular fluid by MATE's 1 and 2 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 with no effect on its urinary recovery (Ae)[4]. This compound is an inhibitor of OCT's 1 and 2-K and MATE's 1 and 2-K (Ki values of 120, 124, 3.8 and 6.9 μM, respectively in HEK293 cells[3]; Ki 11 μM for OCT2 in isolated proximal renal tubules[5]). 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.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 Rowland[6]. For metformin, a permeability-limited liver (PerL) model was used.

Metabolism – A metabolic clearance of metformin was incorporated based on data generated in recombinant human CYP3A4[7], 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[3] and OCT2 and MATEs 1 and 2-K[3], respectively, and in Mech KiM for transport of cimetidine by OCT2[8], OAT3[8,9], MATE1[10,11] and MATE2-K[10]. In the absence of relative activity/expression factors (RAF/REF) for HEK293 cells, 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 PAMPA[12] and human jejunal[13] 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[14].

Trial design – Simulations were performed to evaluate the impact on metformin AUC and amount excreted 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 vivo* study of the metformin – cimetidine interaction[4] 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 studies[3] (*Scenario 3*)
- OCT2 Ki value from fresh proximal tubule cells[5] (*Scenario 4*)
- OCT2 Ki obtained by sensitivity analysis (*Scenario 5*)
- OCT1 and OCT2 Ki values obtained by sensitivity analysis (*Scenario 6*)

Note. For Scenarios 4 to 6 cimetidine Ki's for MATE inhibition were maintained at HEK293 values.

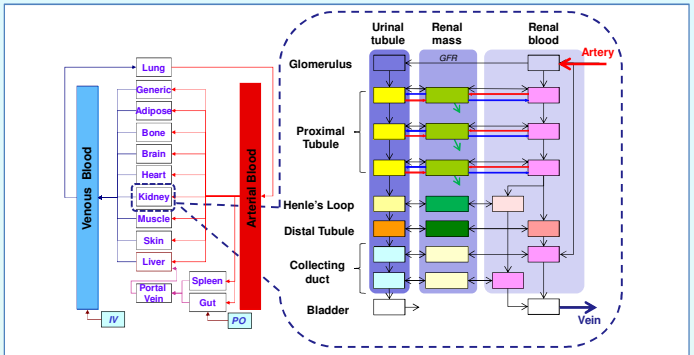

Figure 1 *- The mechanistic kidney model (Mech KiM) as a component of the full PBPK model within Simcyp v.12. Passive processes are represented by black arrows; metabolic, active uptake and efflux processes in the proximal tubule segments are represented by green, blue and red arrows, respectively.*

Results

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 was recovered 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.
- Equipotent 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*).

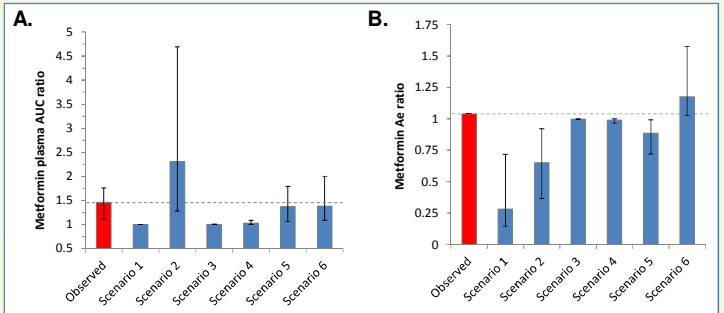

Figure 2 *– Observed metformin AUC (A) and Ae (B) ratios resulting from interaction with cimetidine, and predictions of the ratios under different assumptions with respect to inhibition of metformin transport (The different Scenarios are described under* ***Methods****).*

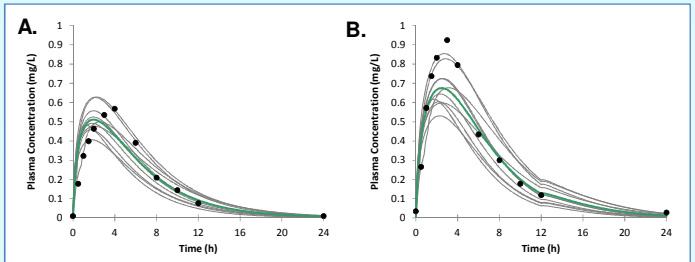

Figure 3 *– Observed (data points[4]) and simulated (lines) plasma metformin concentrations after oral administration (250 mg) with (A) and without (B) co-administration of cimetidine (400 mg BID) (Scenario 5 – OCT1 Ki = 0.5). The grey lines represent the results of 10 virtual trials and the green line is the mean for all individuals.*

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 DDI 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 stimulated is consistent with a decreased hepatic availability for the metabolism of metformin.

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