Evaluation of the drug-drug interaction between Zidovudine and Probenecid by using a mechanistic kidney model (Mech KiM) nested within a full physiologically based pharmacokinetic (PBPK) model

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Background

Zidovudine (AZT) undergoes glucuronidation by UGT2B7 (65-75% of a dose) and 15-20% is eliminated unchanged in the urine. As active tubular secretion contributes significantly to the renal elimination, drug interactions of transporter-mediated uptake in the kidney should be considered in parallel to metabolic drug-drug interactions (DDIs).

Objectives

The aim was to build a mechanistic PBPK model describing the metabolic and renal components of zidovudine elimination and to investigate the effect of probenecid on UGT2B7-mediated metabolism of zidovudine and Organic Anion Transporter 1 (OAT1) uptake in the kidney.

Methods

Zidovudine and Probenecid PBPK models

In vitro information on the permeability, metabolism and transporter kinetics for OAT1 of zidovudine were combined with physicochemical data in a full PBPK model (Simcyp Population-based Simulator Version 14), which included a permeability-limited model for the kidney (Mech KiM) (Figure 1). In addition to hepatic and renal metabolism, renal secretion and reabsorption described by optimised transporter kinetics were also accounted for.

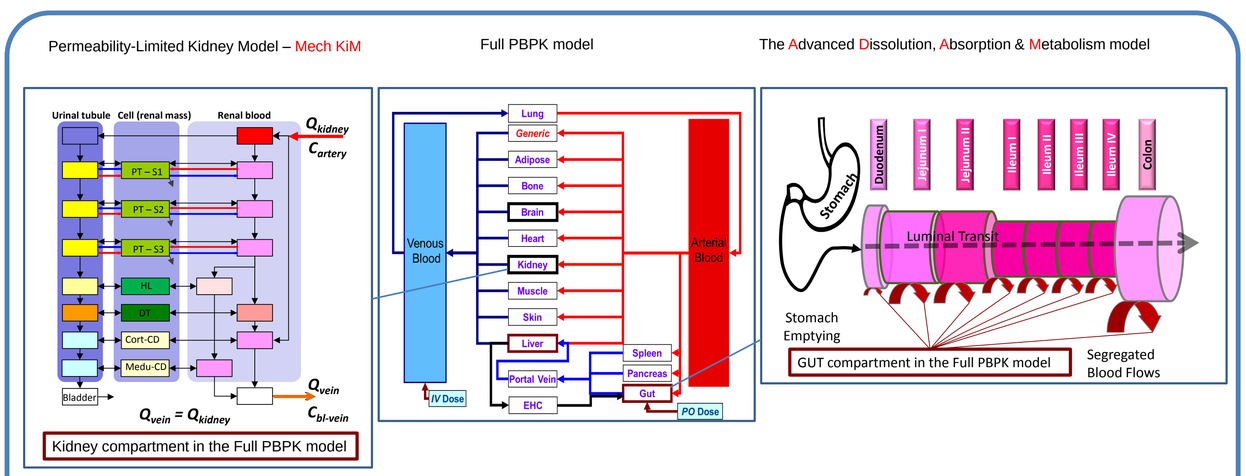

Figure 1. *The full PBPK model within Simcyp V14R1 and the permeability-limited models for gut and kidney. The full PBPK model was used for both compounds with Mech KiM used for zidovudine and ADAM used for probenecid.*

Simulations were run to generate plasma concentration profiles of zidovudine following single doses in healthy volunteers, asymptomatic HIV positive subjects and AIDS patients.

A full PBPK model was also developed for the UGT2B7 and OAT1 inhibitor probenecid. The ADAM (Advanced Dissolution, Absorption and Metabolism) model was utilised to describe the absorption for this compound (Figure 1). Reported *in vivo* CL_{iv} and CL_R were used to back-calculate a metabolic intrinsic clearance using a retrograde approach. Due to the lack of *in vitro* fm data this was assigned as an additional human liver microsomal CL_{int} within the model. Simulations were run to generate plasma concentration profiles of probenecid at the inhibitor dose of 500 mg.

DDI study

In vitro K_i data relating to inhibition of OAT1 in the kidney (Jung *et al.* 2001, Chu *et al.* 2007) were incorporated into the probenecid model. As *in vitro* UGT2B7 K_i values were not available in the literature the UGT2B7 K_i was optimised using a zidovudine interaction study from Hedaya *et al.* 1985. The models were then used to investigate the effects of probenecid (500mg q.i.d. for 2 days) on the exposure of zidovudine (2mg/kg t.i.d. for 2 days) as described by de Miranda *et al.* 1989.

Results

PK profiles of zidovudine and probenecid

The simulated plasma concentration profiles of zidovudine were consistent with observed data in the 3 different groups of subjects (Figures 2A, B and C). Pharmacokinetics of zidovudine are consistent in healthy volunteers and HIV positive patients with normal liver and kidney function (Bareggi *et al.* 1994). Predicted CL_R values were consistent with those reported by Sahai *et al.* 1984 after a 200mg dose (Figure 3A) and simulations recovered the amount excreted unchanged in urine and associated variability after a 100mg dose (Figure 3B) (Ruhnke *et al.* 1993). The simulated plasma concentration profiles for probenecid were consistent with observed data from 2 independent studies at a dose of 500 mg (Figure 4).

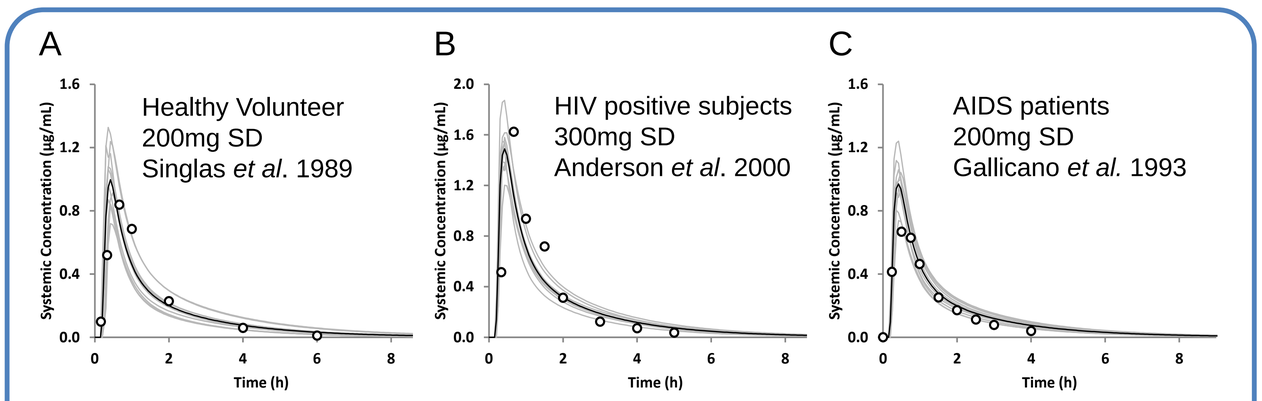

Figure 2. *Simulated (black line) and observed (data points) mean plasma concentration profiles of zidovudine after a single oral dose to (A) healthy volunteers, (B) asymptomatic HIV positive subjects and (C) AIDS patients. The grey lines represent predictions from 10 individual trials.*

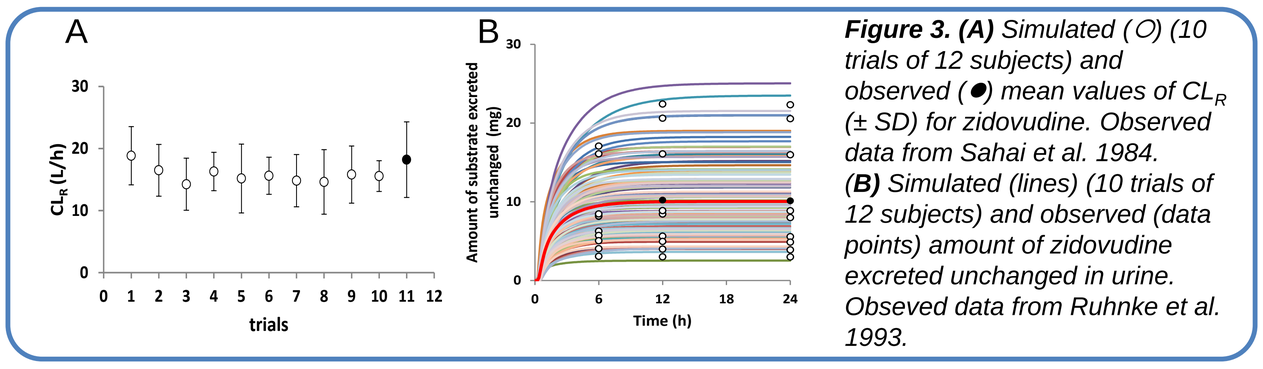

Figure 3. (A) *Simulated (○) (10 trials of 12 subjects) and observed (●) mean values of CL_R (± SD) for zidovudine. Observed data from Sahai et al. 1984.* ***(B)*** *Simulated (lines) (10 trials of 12 subjects) and observed (data points) amount of zidovudine excreted unchanged in urine. Obseved data from Ruhnke et al. 1993.*

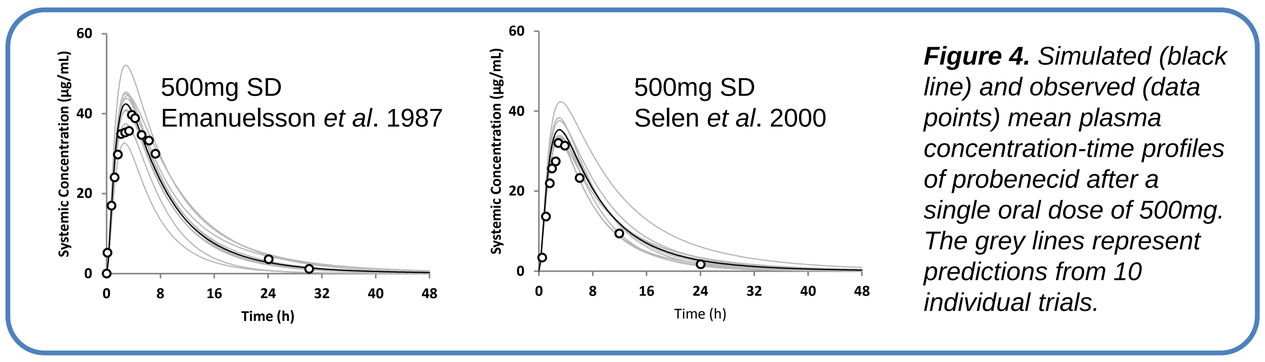

Figure 4. *Simulated (black line) and observed (data points) mean plasma concentration-time profiles of probenecid after a single oral dose of 500mg. The grey lines represent predictions from 10 individual trials.*

UGT2B7 and OAT1-mediated DDI

The predicted concentration-time profiles, indicating the increase in exposure of zidovudine following administration of probenecid, were consistent with observed data (Figure 5). The mean predicted and observed AUC ratios were 1.97 (trial range 1.65 - 2.18) and 2.06 respectively. Ratios of C_{max} were 1.51 (trial range 1.43 – 1.56) and 1.43 respectively. The predicted decrease in renal clearance after probenecid treatment was similar to observed (Figure 6). Simulation of the DDI excluding OAT1 inhibition predicted AUC and C_{max} ratios of 1.64 and 1.39, respectively, with no change in renal clearance.

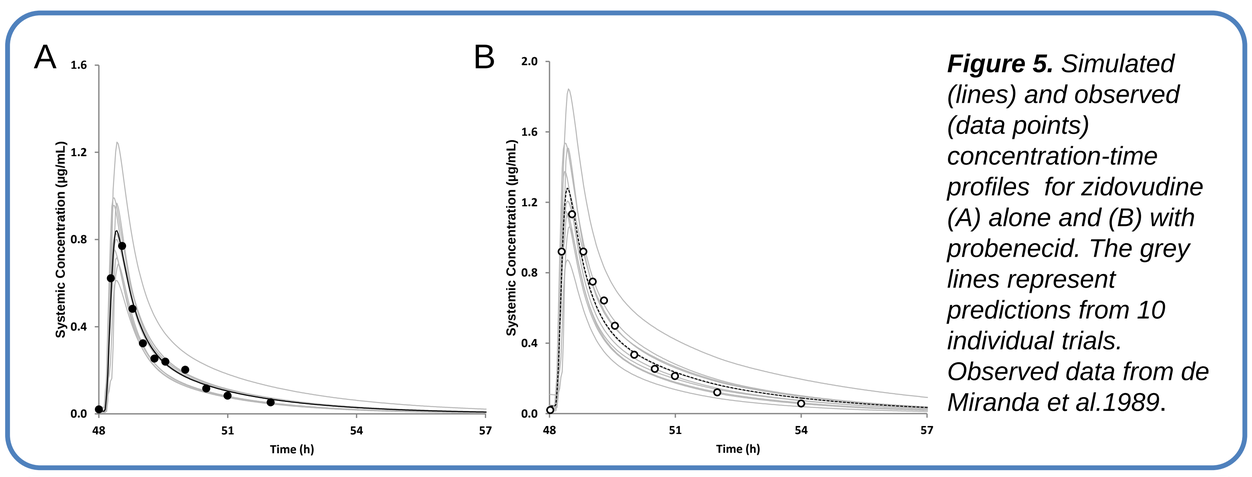

Figure 5. *Simulated (lines) and observed (data points) concentration-time profiles for zidovudine (A) alone and (B) with probenecid. The grey lines represent predictions from 10 individual trials. Observed data from de Miranda et al.1989.*

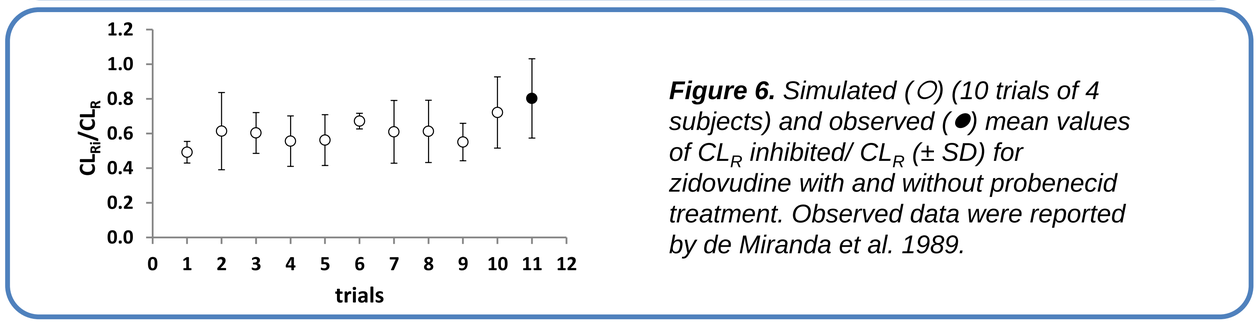

Figure 6. *Simulated (○) (10 trials of 4 subjects) and observed (●) mean values of CL_R inhibited/ CL_R (± SD) for zidovudine with and without probenecid treatment. Observed data were reported by de Miranda et al. 1989.*

Conclusions

- PBPK modelling in conjunction with reliable *in vitro* data can be used to assess the importance of interactions affecting both metabolism and transport.
- Incorporation of Mech KiM within a full PBPK model for zidovudine allows mechanistic prediction of excretion in the kidney and simultaneous assessment of metabolism and transporter interactions with probenecid.
- Inhibition of UGT2B7-mediated metabolism appears to be a more significant determinant of the DDI than inhibition of renal clearance.

References

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