Simultaneous inhibition of glucuronidation and renal transporter pathways; a mechanistic evaluation of the interaction between zidovudine and probenecid using physiologically based pharmacokinetic (PBPK) modelling

Sibylle Neuhoff, H. Kim Crewe & Karen Rowland Yeo

Simcyp (A Certara Company), Sheffield, UK

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 disposition of zidovudine elimination to investigate the inhibitory effects 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), with a nested permeability-limited model for the kidney (Mech KiM) (Figure 1). In addition to hepatic and renal metabolism (UGT2B7), renal filtration, saturable (OAT1) and non-saturable secretion and reabsorption were also considered.

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

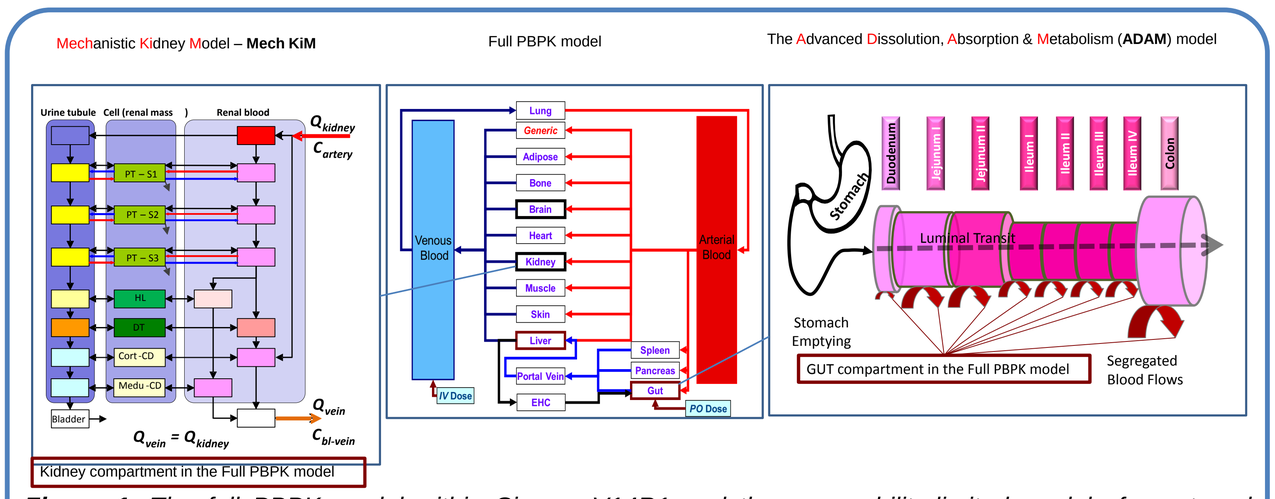

Figure 1. *The full PBPK model within Simcyp V14R1 and the permeability-limited models for gut and kidney. The full PBPK model was used for both compounds with Mech KiM used for zidovudine and ADAM used for probenecid.*

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. As *in vitro* enzymology data were not available, an additional human liver microsomal CL_{int} was assigned for the metabolism. 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, a value was derived using a zidovudine interaction study from Hedaya *et al.* 1985. Both PBPK models were applied 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) using the clinical study described by de Miranda *et al.* 1989.

Results

PK profiles of zidovudine and probenecid

- The simulated plasma concentrations 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 of zidovudine 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 concentrations for probenecid were consistent with observed data from 2 independent studies at a dose of 500 mg (Figure 4).

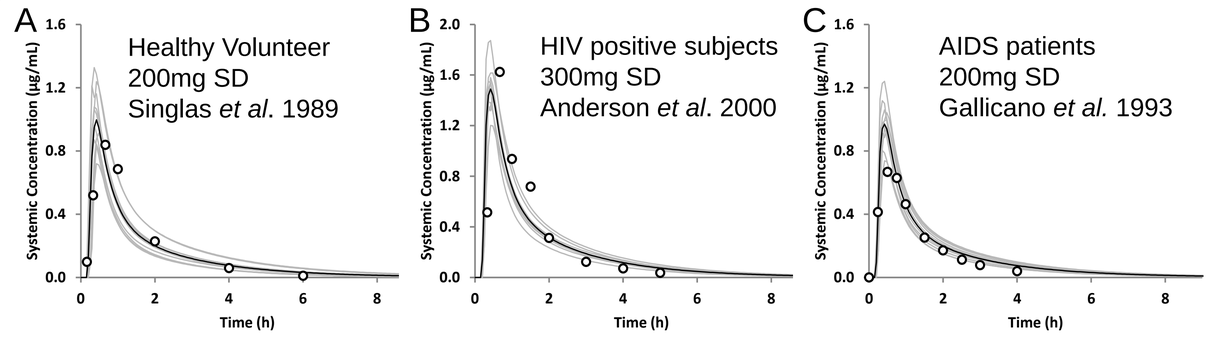

Figure 2. *Simulated (black line) and observed (data points) mean plasma concentration profiles of zidovudine after a single oral dose to* ***(A)*** *healthy volunteers,* ***(B)*** *asymptomatic HIV positive subjects and* ***(C)*** *AIDS patients. The grey lines represent predictions from 10 individual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

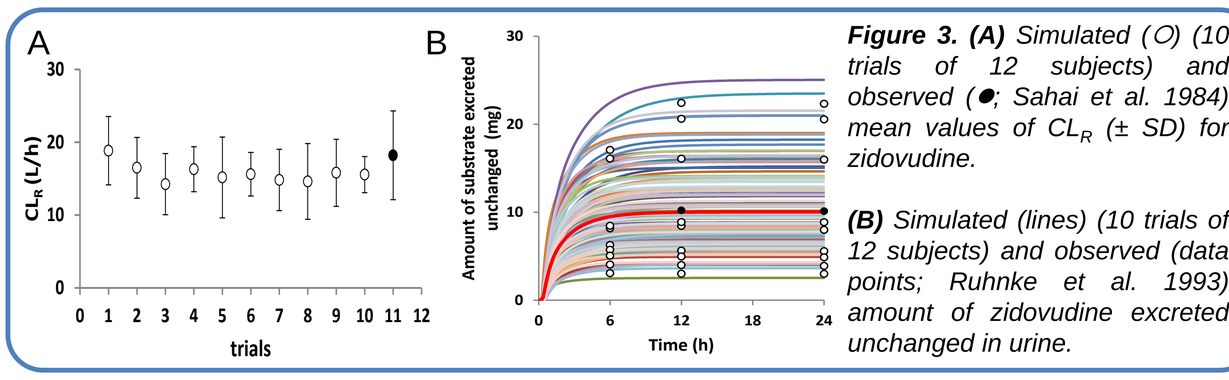

Figure 3. (A) *Simulated (○) (10 trials of 12 subjects) and observed (●; Sahai et al. 1984) mean values of CL_R (± SD) for zidovudine.*

(B) *Simulated (lines) (10 trials of 12 subjects) and observed (data points; Ruhnke et al. 1993) amount of zidovudine excreted unchanged in urine.*

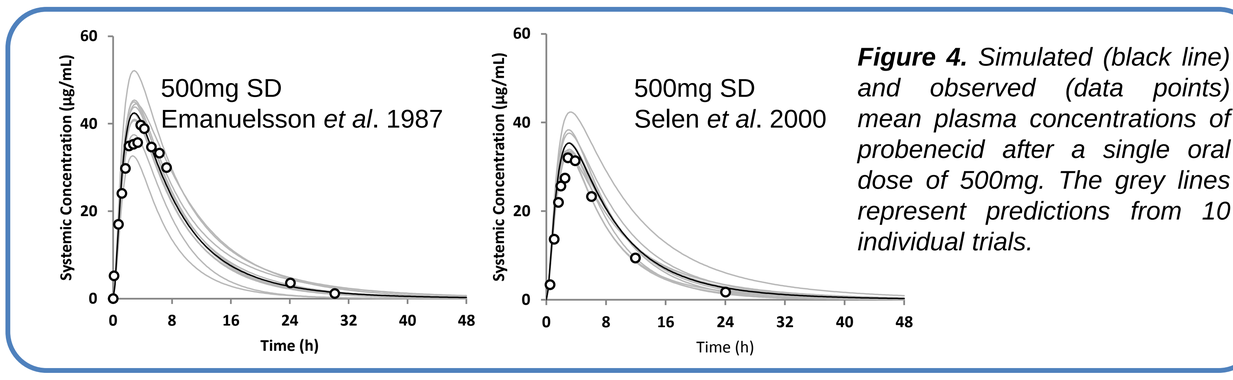

Figure 4. *Simulated (black line) and observed (data points) mean plasma concentrations of probenecid after a single oral dose of 500mg. The grey lines represent predictions from 10 individual trials.*

UGT2B7 and OAT1-mediated DDI

The predicted increase in exposure of zidovudine following co-administration of probenecid was 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.

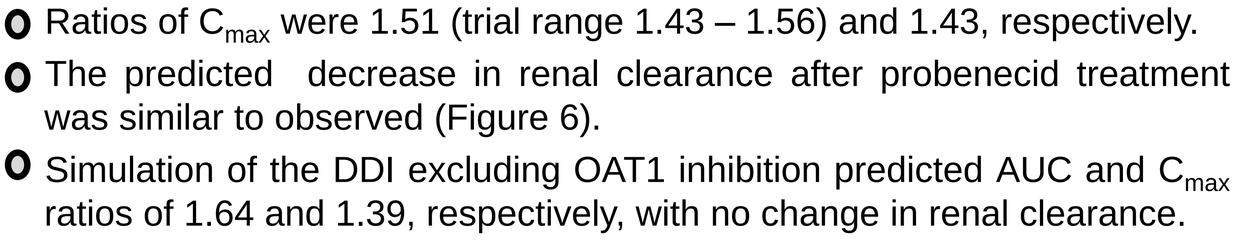

Figure 5. *Simulated (lines) and observed (data points; de Miranda et al.1989) concentration-time profiles for zidovudine* ***(A)*** *alone and* ***(B)*** *with probenecid. The grey lines represent predictions from 10 individual trials.*

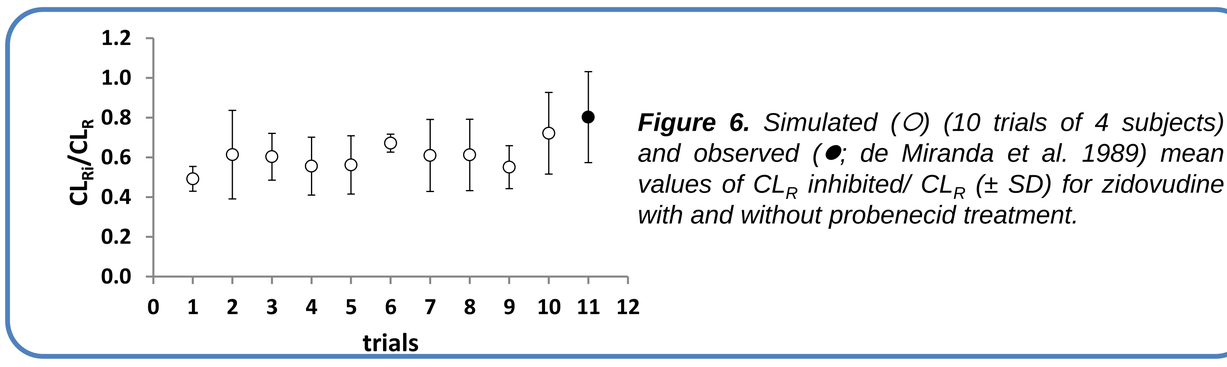

Figure 6. *Simulated (○) (10 trials of 4 subjects) and observed (●; de Miranda et al. 1989) mean values of CL_R inhibited/ CL_R (± SD) for zidovudine with and without probenecid treatment.*

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

Anderson *et al.* 2000. Pharmacotherapy 20: 917-922
Bareggi *et al.* 1994. JCP 34: 782-786
Chu *et al.* 2007. JPET 321: 673-683
de Miranda *et al.* 1989. CPT 46: 494-500
Emanuelsson *et al.* 1987. EJCP 32: 395-401
Gallicano *et al.* 1993. Br J Clin Pharmacol 36:128-131
Hedaya *et al.* 1985. Pharm Res 7: 411-417
Jung *et al.* 2001. Life Sciences 69: 2123–2135
Ruhnke *et al.* 1993. Antimic Agents Chemother. 37: 2153-2158
Sahai *et al.* 1984. J Infectious diseases 169:1103-1107
Singlas *et al.* 1989. EJC P 36: 639-640
Selen *et al.* 1982. JPS 71: 1238-1242

Presented at the Biomedical Transporter meeting, August 2015, Lugano, Switzerland