ASSESSMENT OF THE INDUCTION OF SYSTEMIC CLEARANCE *VS*. FIRST-PASS METABOLISM OF MIDAZOLAM BY RIFAMPICIN USING A PHYSIOLOGICALLY-BASED DYNAMIC MODEL

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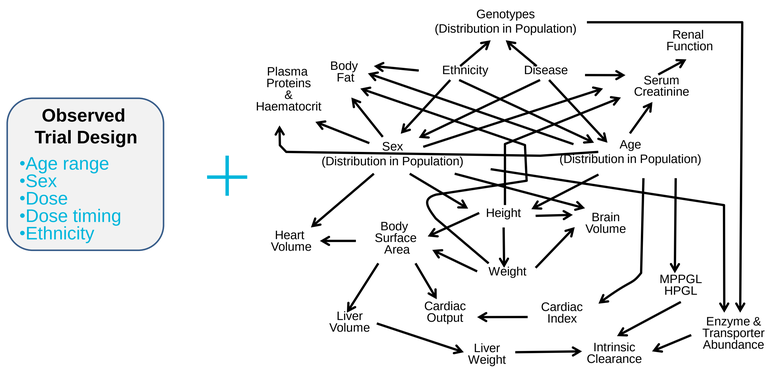
BACKGROUND

- Dynamic models considering multiple simultaneous interaction mechanisms (*e.g.* inhibition and induction) over time can be used to investigate dosing strategies in therapeutic areas where drug combinations are the standard of care.
- The dynamic physiologically-based pharmacokinetic (PBPK) model in the Simcyp Simulator uses *in vivo* reference data on rifampicin (RIF) to calibrate *in vitro* induction data.
- We have assessed the performance of this model by comparing the predictions with observed drug-drug interactions (DDIs) using RIF as perpetrator and midazolam (MDZ) as victim. Potential sources of discrepancy between predicted and observed outcome were investigated.

METHODS

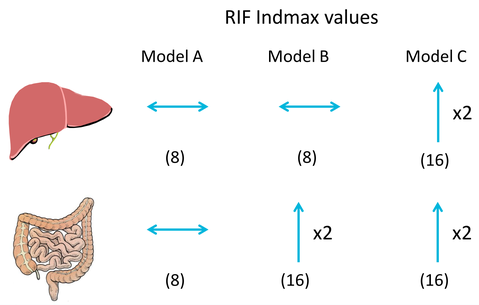
- Literature searches in (PubMed, University of Washington Database) were used to identify relevant clinical DDI studies.
- Simulated populations (Simcyp V10.1) were matched to reported populations in each clinical study (simulation trial design) and generated based on the co variation (Figure 1) between demography (*e.g.* age, sex) and physiological parameters (*e.g.* an individual's liver size or plasma albumin concentration). Default values for RIF and MDZ saved within the simulator's databases were used (Base Model A; Figure 2).

Figure 1 Virtual subjects are generated based on the relationships of covariates affecting ADME defined within the Simulator databases and user-defined trial design.



- AUC ratios were calculated as $AUC_{control}/AUC_{induced}$ to give ratios > 1. Fold Error (FE) was calculated as [observed AUC ratio– 1] /[predicted AUC ratio -1]) to avoid bias associated with comparing two ratios. These were used to asses the accuracy of the base model and its subsequent adaptations.
- Additional clinical studies describing the exposure of 2 other CYP3A4 substrates (simvastatin, SMV; nifedipine, NIF) before and after RIF administration were identified and also used to assess the accuracy of predictions.

Figure 2 Schematic overview of the RIF Indmax values (in parentheses) for CYP3A4 in the liver and gut in the base Model A and the modified Models B and C



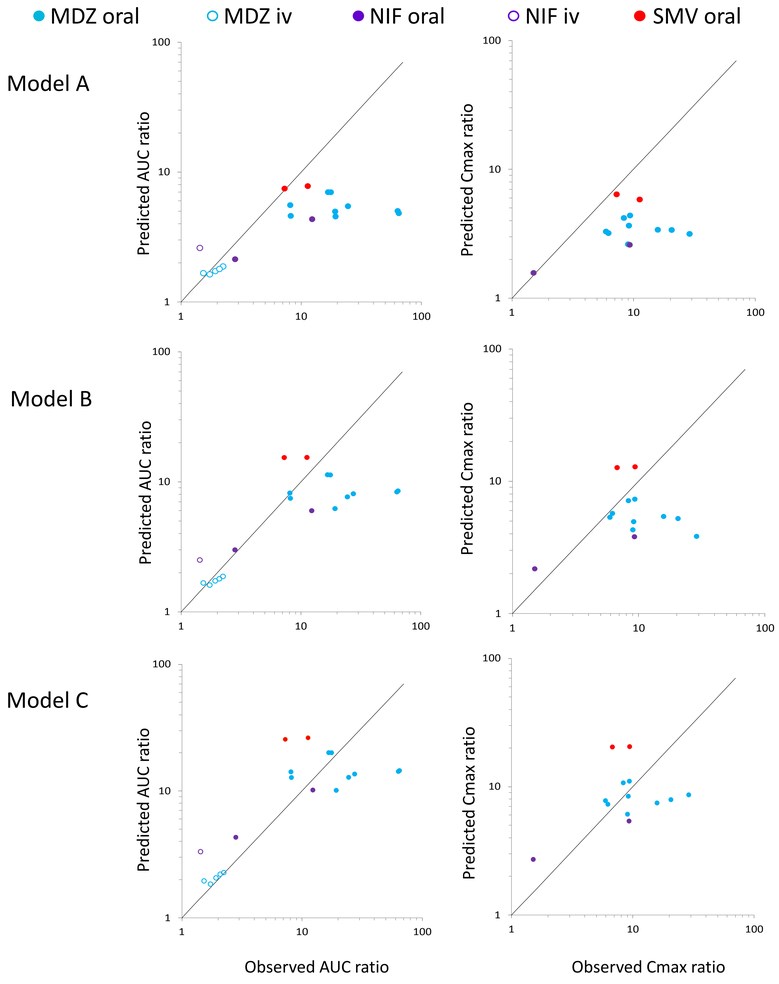
METHODS CONT.

- Two alternative models for RIF induction with B) 2-fold increase in maximum fold induction (Indmax) for gut alone (induction of E_G) or C) 2-fold increase in Indmax for gut and liver induction of E_G, E_H and CL) were then assessed (Figure 3).

RESULTS

- Fourteen clinical studies describing MDZ exposure (5 IV and 9 oral) before and after RIF administration were identified (Table 1).
- The magnitude of DDI was larger and more variable (range 7.2-64.3) when MDZ is given orally compared to IV (range 1.5-2.2).
- The extent of DDI with IV MDZ was accurately described by the model (FE range 0.7-1.4), however, the AUC ratios predicted for oral MDZ show under prediction (FE range 1.7-17.9; Figure 2).
- Under prediction was reduced when either the Indmax for gut alone was increased (FE 0.94-8.4) or when Indmax for both gut and liver were increased (FE 0.6-4.7) with marginal changes in the accuracy of DDI predictions with IV MDZ (Figure 3).

Figure 3 Comparison of observed and predicted AUC and Cmax ratios when A) Indmax for liver and gut =8 (base model) B) Indmax for liver = 8 and gut = 16 and C) Indmax for liver and gut =16.



RESULTS CONT.

- Recovery of DDIs where SMV was given as the victim drug were most accurately described with the base model (FE 1.1, 1.5) *vs.* the model with increased Indmax for the gut (FE 1.4, 2.3) *vs.* increased Indmax for gut and liver (FE 2.5, 3.9; Figure 3).

Table 1 Comparison of observed and predicted AUC and Cmax ratios.

Dosing Regimen					AUC ratios			Cmax ratios			
RIF	MDZ (single dose)	MDZ RoA	n	Dose Stagger (h)	obs	pred	FE	obs	pred	FE	Ref
600 mg *q.d.* 5d	1 mg	IV	6	12	2.0	1.9	1.1				1
600 mg *q.d.* 7d	0.05 mg/kg	IV	52	12	2.1	1.7	1.4				2
600 mg *q.d.* 5d	1 mg	IV	10	12	1.9	1.6	1.4				3
600 mg *q.d.* 7d	0.05 mg/kg	IV	3	12*	1.7	1.7	1.1				4#
600 mg *q.d.* 6d	2 mg	IV	8	24	1.5	1.7	0.7				5
600 mg *q.d.* 5d	15 mg	oral	10	17	24	5.9	4.8	16	3.9	5.1	6
600 mg *q.d.* 5d	15 mg	oral	9	17	63	5.7	13	20	3.8	6.9	7
600 mg *q.d.* 5d	3 mg	oral	10	12	19	5.6	3.9	9.1	3.7	3.0	3
450 mg *q.d.* 5d	7.5 mg	oral	4	12	19	4.4	5.4	9.0	3.2	3.6	8
600 mg *q.d.* 9d	0.075 mg/kg	oral	18	-2	8.0	5.3	1.7	5.9	3.8	1.8	9
300 mg *b.d.* 7d	8 mg	oral	19	0*	18	4.8	4.3	8.3	3.4	3.1	10
300 mg *b.d.* 7d	8 mg	oral	16	2	17	7.9	2.3	9.3	4.4	2.4	11
600 mg *q.d.* 6d	7.5 mg	oral	8	24	64	4.6	17.9	28	3.6	10	5
600 mg *q.d.* 28d	2 mg	oral	11	0	8.1	5.2	1.7	6.2	3.7	1.9	12

RoA: route of administration
Dose Stagger: the time after RIF dosing when MDZ was given. A negative value indicates MDZ was given prior to RIF last dose
 # study was carried out in patients rather than healthy volunteers
**Ambiguous*

CONCLUSIONS

- Despite fairly homogenous study design, there is extensive variability in the DDI ratios across studies when MDZ (oral) was used as the victim drug. The relative paucity of RIF studies with other victims in the literature makes it difficult to ascertain if this is MDZ-specific.
- The accurate prediction of DDI following IV but not oral MDZ dosing suggests good recovery of induction in the liver by the existing model but questions the assumptions related to elements of induction of first-pass in gut and liver.
- Calculation of E_H after induction (mean 0.6; range 0.27-0.79) for clinical IV studies suggests that capacity limitation *in vivo* is not 'capping' the induction when MDZ is given intravenously.
- Initial studies investigating if disproportionate changes in F_H (*e.g.* displacement of MDZ from plasma protein in the portal vein during absorption) or F_G (*e.g.* different E_{max} in liver *vs.* Gut) relative to systemic clearance drives the under prediction observed when MDZ is given orally are ongoing. However, comparison of the dose stagger adopted across clinical trials suggests that displacement is an unlikely explanation.
- It is known that rifampicin induces CYP3A in enterocytes[12] however, studies characterising Indmax and EC_{50} in donor matched enterocytes and hepatocytes are required assess the relative efficacy and potency of RIF induction in the different tissues.

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