USE OF A PBPK APPROACH TO ASSESS THE RISK OF DRUG INTERACTIONS IN DIABETIC PATIENTS ON POLYPHARMACY TREATMENT REGIMENS

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Background

Most patients with type-2 diabetes are often on polypharmacy treatment regimens due to the presence of cardiovascular related co-morbidities. The exposure of each prescribed drug could be altered as a result of the interplay between diabetes-related physiological changes and any potential impact of the co-administered drugs. Physiologically based pharmacokinetic (PBPK) models provide a framework to modify the physiological status of virtual subjects to match the characteristics of a given disease population. With this information included the pharmacokinetics of co-administered drugs as well as any drug-drug interactions in different scenarios, not easily explored in clinical studies, can be simulated.

Method- Model Development

A virtual population of type-2 diabetic patients was developed in the Simcyp® simulator V17R1, that incorporated the following differences to a default healthy volunteer (HV) population: age and sex distribution; and percentage of obese individuals (Figure 1a); with the associated obese-related modified tissue blood flows, composition and metabolic enzyme changes[1]. The diabetic population was verified by predicting the PK of three anti-diabetic drugs (Glibenclamide, Metformin and Repaglinide) administered to virtual Type-2 diabetic patients (Figure 1b) with a trial design replicating that described in the respective clinical studies[2,3,4].

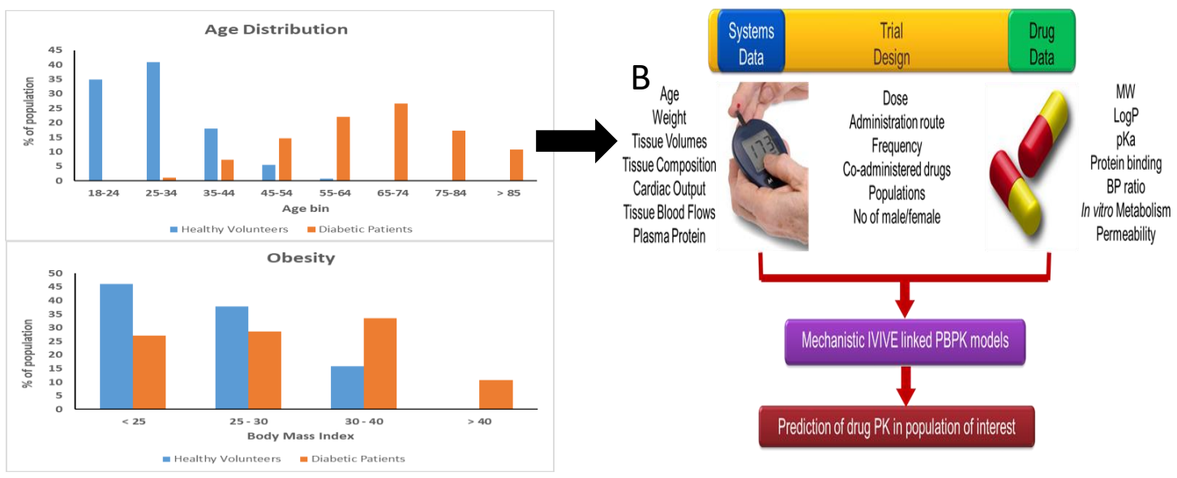

Figure 1: Schematic showing how the differences in the demographics of a diabetic population from that of a healthy volunteer population can be incorporated into a mechanistic PBPK model and used to predict the PK of various drugs based on different clinical study trial design.

Method- Model Application

To assess the combined effect of diabetes-related physiological changes and drugs co-administered to type-2 diabetic patients, twelve drugs from three therapeutic areas often present in type-2 diabetic patients were identified (Figure 2). Combinations of these drugs (Table 1) based on an assessment of drugs with a known risk of causing pharmacokinetic drug-drug interactions (highlighted red in Figure 2) were simulated in the Simcyp® simulator using the virtual Caucasian diabetic population and the default HV population.

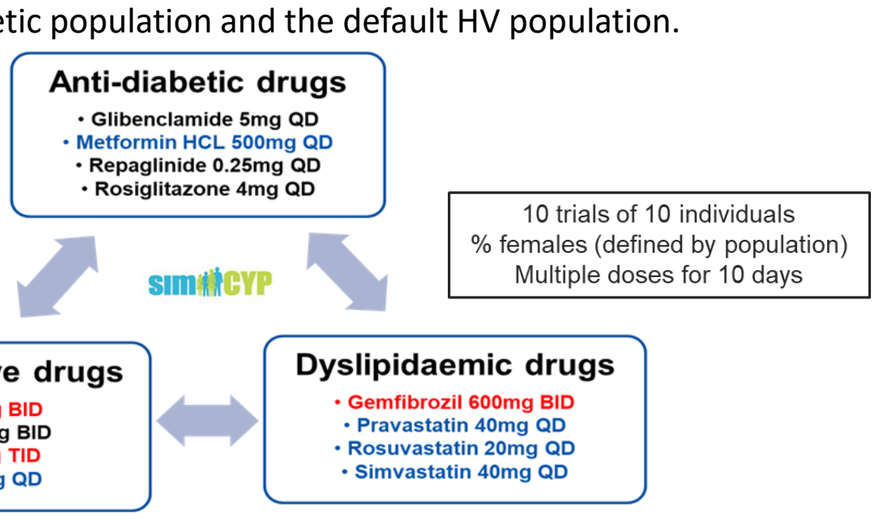

Figure 2: Combinations of drugs from each therapeutic area, representing a possible treatment regimen were simulated in the Simcyp® simulator to assess the combined effect of polypharmacy & diabetes-related physiological changes on each drug's PK.

Diabetic nephropathy is one of the most serious long term microvascular complications of diabetes and one of the leading causes of end-stage renal disease (ESRD)[5]. The impact of a severely impaired renal function on the predicted PK of four drugs with a significant renal clearance component (highlighted blue in Figure 2) were also assessed using a modified diabetic population in which the glomerular filtration rate (GFR) had been adjusted to less than 30 ml/min/1.73m^2.

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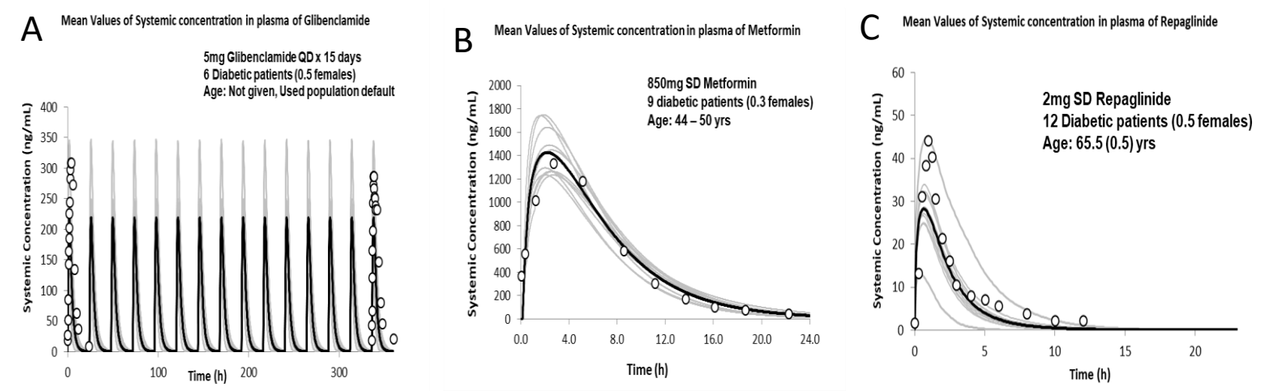
Results: Model Verification

The observed data of glibenclamide, metformin and repaglinide from the replicated clinical studies were reasonably recovered using the virtual diabetic population as shown in Figure 3 below.



	Cmax-Day 15 (ng/mL)	AUC-Day 15 (ng/mL.h)
Population mean (stdev)	224.55 (68.23)	NA
Observed mean (stdev)	286.57	1044.63 (422.69)

	CMax (µg/mL)	AUC_INF (µg/mL.h)
Population mean	1.46	11.37
Observed mean	1.49	11.65

	CMax (ng/mL)	AUC (ng/mL.h)
Population mean (stdev)	28.7 (10.08)	84.54 (52.03)
Observed mean (stdev)	56.5 (23.3)	117.9 (83.8)

Figure 3: Simulated (black line) mean plasma concentration time profile of (A) glibenclamide, (B) metformin and (C) repaglinide in type-2 diabetic patients. The grey lines represent the predictions from individual trials and the data points represent observed data from the respective clinical studies[2,3,4].

Results: Model Application

Table 1: Predicted AUC and Cmax ratios of the substrate drug in the healthy volunteer and the diabetic populations when co-administered as part of different treatment regimens.

	Substrate	Perpetrator 1	Perpetrator 2	Healthy Volunteer Population		Diabetic Population	
				AUC ratio	Cmax ratio	AUC ratio	Cmax ratio
1	Simvastatin	Verapamil (& Nor-verapamil)	Any of the anti-diabetic drugs	16.81	9.93	20.4	10.79
2	Repaglinde	Gemfibrozil (& Gemfibrozil glucuronide)	Verapamil	11.22	3.35	21.02	4.8
3	Repaglinde	Gemfibrozil (& Gemfibrozil glucuronide)	Nifedipine	5.92	2.49	7.68	2.72
4	Repaglinde	Gemfibrozil (& Gemfibrozil glucuronide)	Valsartan or Metoprolol	5.81	2.45	7.42	2.66
5	Rosiglitazone	Gemfibrozil (& Gemfibrozil glucuronide)	Any of the anti-hypertensive drugs	2.58	1.27	1.73	1.03
6	Glibenclamide	Gemfibrozil (& Gemfibrozil glucuronide)	Verapamil	2.04	1.52	2.23	1.53
7	Glibenclamide	Gemfibrozil (& Gemfibrozil glucuronide)	Valsartan or Metoprolol	1.94	1.46	2.08	1.46
8	Valsartan	Gemfibrozil (& Gemfibrozil glucuronide)	Any of the anti-diabetic drugs	1.38	1.3	1.47	1.32
9	Glibenclamide	Gemfibrozil (& Gemfibrozil glucuronide)	Nifedipine	1.14	1.06	1.16	1.06
10	Simvastatin	Nifedipine	Any of the anti-diabetic drugs	1.07	1.08	1.08	1.09
11	Glibenclamide	Verapamil (& Nor-verapamil)	Any of the statins	1.07	1.05	1.09	1.06
12	Repaglinide	Nifedipine	Any of the statins	1.02	1.02	1.01	1.01

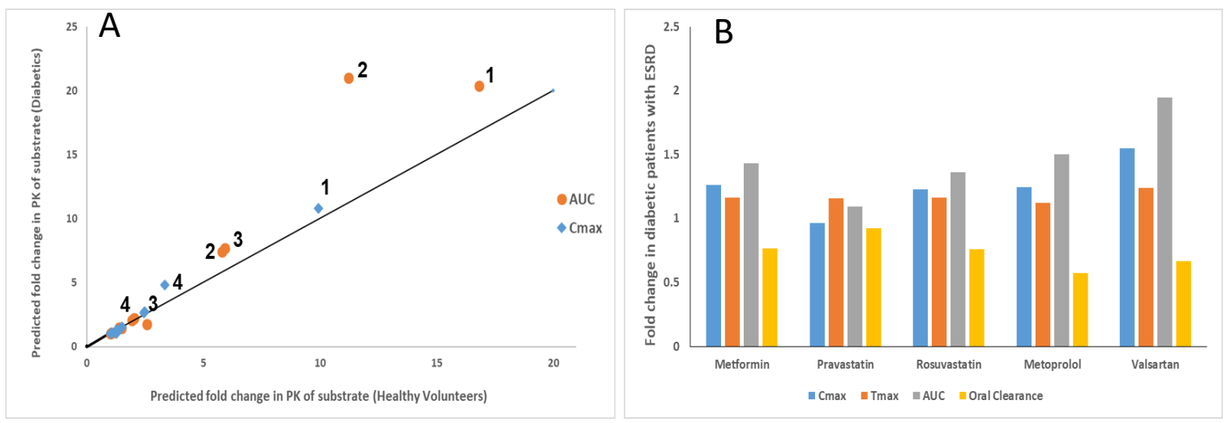


Figure 4: Predicted fold change in the PK of (A) drugs administered as part of a polypharmacy treatment regimen compared to control when drugs are administered alone; and (B) drugs with significant renal clearance administered to diabetic patients with ESRD compared to control PK when administered to a healthy volunteer population.

Discussion

- Clinical drug interaction studies often conducted in HVs do not always provide sufficient information about the PK of the drug in the population of interest. PBPK models can act as a useful tool for predicting possible complex polypharmacy DDIs, not easily explored in clinical trials.
- The virtual diabetic population enabled the simulation of different possible treatment regimens for diabetic patients involving drugs with a known risk of drug interactions. Certain drug combinations can result in a higher DDI risk than others as shown with studies 1 & 2 in Table 1.
- In addition, renal impairment due to diabetic nephropathy can result in up to a 2-fold change in the PK of certain drugs used by diabetic patients.

References

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