

Title: MECHANISTIC MODELS OF HUMAN PHARMACOKINETICS TO PREDICT THE EFFECTS OF LIVER CIRRHOSIS ON THE CLEARANCE OF NINE DRUGS

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Objectives: Regulatory authorities often ask for information on handling of metabolically cleared drug in cirrhotic patients. Ability to predict the effects of cirrhosis on clearance of drugs is desirable if this can help with assessing the requirements and design of studies in this group of patients. Liver cirrhosis is characterized by a reduction in functional hepatocytes, reduced circulating levels of plasma proteins and alterations in blood flow due to development of portosystemic shunts. Thus, depending on the interplay between these parameters and the characteristics of the compound, varying degrees of reduced systemic clearance and a reduced first pass metabolism might be expected.

The Simcyp simulator incorporates genetic, physiological, demographic and clinical attributes of patient populations pertinent to *in vitro-in vivo* extrapolation of xenobiotic metabolism into libraries that can be used for automated prediction of pharmacokinetic parameters including drug clearance (CL) [1].

The objectives of this study were:

- To develop Simcyp population models to predict the steady state clearance of drugs in relation to the severity of liver cirrhosis as defined by the Child-Pugh score.
- To predict the systemic and oral clearance of a range of drugs and to compare the results with *in vivo* data.

Methods: Information on demographics, changes in hepatic blood flow, CYP enzymes, liver size, protein binding, renal function, tissue composition & blood flow, blood volume, organ size and gastric emptying were incorporated in to three separate population models within the Simcyp simulator. These corresponded to Child-Pugh scores A (mild), B (moderate) and C (severe) liver cirrhosis. The drugs studied were midazolam (oral and iv), caffeine (oral), theophylline (oral and iv), metoprolol (oral and iv), nifedipine (oral), quinidine (oral), diclofenac (oral), sildenafil (oral) and omeprazole (oral and iv). *In vitro* V_{max} and K_m values and *in vivo* clearance data for each drug were obtained from the literature. Simulated studies were matched as closely as possible to the clinical studies for demographics and Child-Pugh scores. Simcyp predicted CL values in both healthy control and liver cirrhosis populations were compared with observed values as were ratio of CL values between these populations.

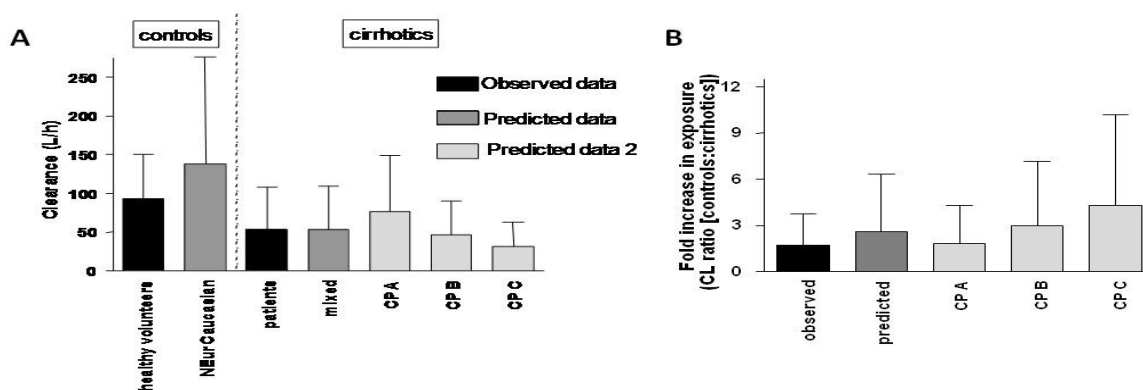


Figure 1. (A) Comparison of observed and predicted CL values for oral midazolam in healthy controls and cirrhotic patients and (B) comparison of the corresponding healthy control vs cirrhosis ratios.

Results: Representative graphs for the absolute CL values for oral midazolam are shown in Figure 1A and the healthy control vs cirrhosis ratios in Figure 1B. The predicted values in pure populations of Child-Pugh A, B and C is shown for reference. Observed and predicted CL ratio in healthy control vs cirrhosis is shown for all drugs in Table 1. There was good agreement between observed and predicted ratios and a statistically significant difference was only seen in the case of iv omeprazole.

Drug	Major enzyme	Control vs cirrhosis ratio		Statistical significance
		Observed	Predicted	
Caffeine (O)	CYP1A2	2.6	2.8	NS
Diclofenac (O)	CYP2C9 / Glucuronidation	2.5	1.6	NS
Metoprolol (IV)	CYP2D6	1.3	2.0	NS
Metoprolol (O)	CYP2D6	2.7	2.5	NS
Midazolam (IV)	CYP3A4	1.8	1.7	NS
Midazolam (O)	CYP3A4	1.7	2.6	NS
Nifedipine (O)	CYP3A4	2.1	2.7	NS
Omeprazole (IV)	CYP2C19	8.2	2.0	P<0.05
Omeprazole (O)	CYP2C19	3.4	3.9	NS
Quinidine (O)	CYP3A4	1	1.8	NS
Sildenafil (O)	CYP3A4	1.8	1.9	NS
Theophylline (IV)	CYP1A2	2.0	2.3	NS
Theophylline (O)	CYP1A2	1.7	2.5	NS

Conclusions: Overall there was good prediction of the effects of liver cirrhosis on drug clearance despite the diversity among the compounds tested. Prediction of such covariate effects are useful in the drug development process as they allow an assessment of the likely dose adjustment necessary before starting clinical studies as well as design of population pharmacokinetics studies.

References:

[1] Tucker GT, Rostami-Hodjegan A, Simulation and Prediction of *in vivo* metabolic drug clearance from *in vitro* data. Nature Reviews Drug Discovery 2007; 6: 140-148.