PREDICTION OF THE INCREASED EXPOSURE TO DRUGS IN LIVER CIRRHOSIS: A SYSTEMS BIOLOGY APPROACH INTEGRATING PRIOR INFORMATION ON DISEASE WITH *IN VITRO* DATA ON DRUG DISPOSITION

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INTRODUCTION

Liver cirrhosis is the end stage of every chronic liver disease, and is associated with many physiological and biological changes that may alter pharmacokinetics (PK) (Figure 1). These include a decrease in the number of functional hepatocytes, lower concentrations of plasma proteins, alterations in blood flow (e.g. portacaval shunts), variable decreases in CYP450 activities, and alterations in body composition. The interplay between these changes and the specific PK properties of a drug determines the magnitude and direction of any variation in its systemic clearance (CL) as well as the first pass gut and liver metabolism.

Regulatory authorities require information on the effects of cirrhosis on the kinetics of metabolically cleared compounds. The ability to anticipate such effects and to estimate their likely impact should facilitate the selection and design of *in vivo* studies. In this context, the Simcyp Population-Based ADME Simulator [1] is used:

- To capture and integrate physiological and biological information relevant to ADME in liver cirrhosis (defined by the Child-Pugh (CP) score),
- To predict the systemic and oral CL of drugs in cirrhosis based on *in vitro* data.

METHODS

Information on demographics, organ blood flows, CYP enzymes, size of liver and other organs, plasma protein concentrations, renal function, tissue composition, volume of blood, and gastric emptying in liver cirrhosis were collated from the literature and, after appropriate analysis, incorporated into the "population libraries" of the Simcyp simulator (v8). Separate libraries were built corresponding to CP scores A (mild), B (moderate) and C (severe). 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* Vmax and Km values for each drug were default values in Simcyp compound libraries [2], *in vivo* data were from the literature. Virtual populations were matched as closely as possible to those used in the actual clinical studies (demographics and proportion of patients within each CP score). CL values in both healthy controls and patients with liver cirrhosis were predicted and compared with observed values.

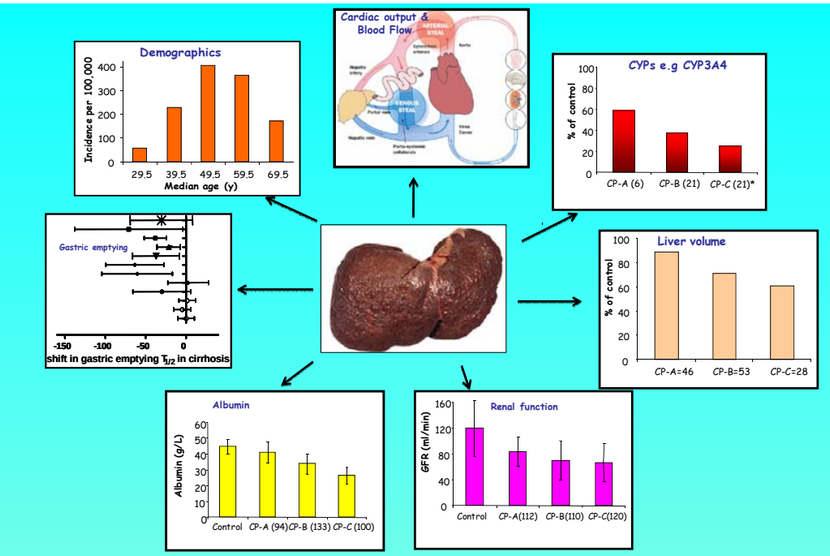

Figure 1. Major changes in patients with liver cirrhosis pertinent to changes in pharmacokinetics.

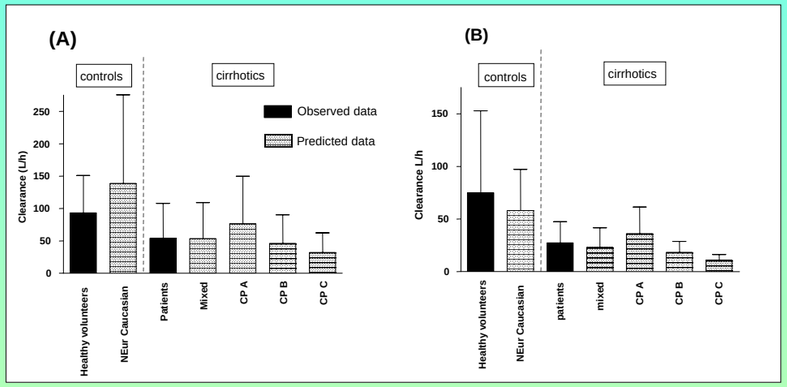

Figure 2. Comparison of observed and predicted oral CL values of (A) midazolam and (B) oral metoprolol in healthy controls and cirrhotic patients

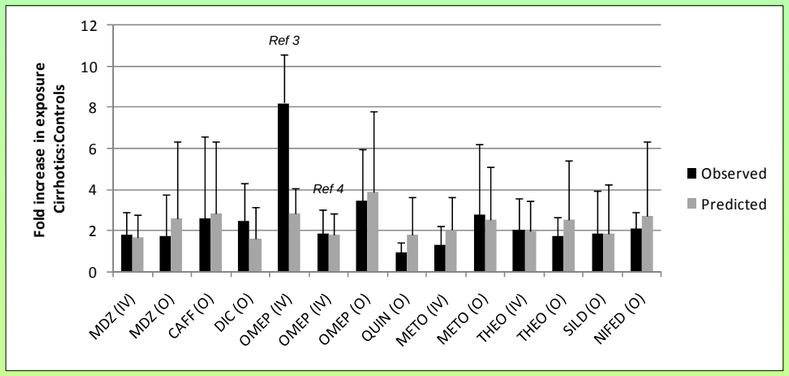

Figure 3. Comparison of observed and predicted fold change in exposure: cirrhosis vs healthy controls (mean ± SD).

RESULTS

Representative data for oral midazolam and metoprolol in healthy control and cirrhotic subjects are shown in Figure 2. Simulations were carried out in a population comprising mixed CP scores as well as in patients with specific CP scores. There was good agreement (lack of statistically significant difference, 2 tail paired t-test) between observed and predicted clearance ratios (Figure 3), with the exception of one study of IV omeprazole ($p < 0.05$). Predicted CL ratios were within 0.8 to 1.25 fold of observed ratios in 57% of cases (range 0.34 – 1.9 fold).

CONCLUSIONS

The effects of liver cirrhosis on drug CL were predicted with reasonable accuracy despite the diversity of the drugs studied. In the case of omeprazole, the outcome of one study was predicted successfully but that from another was not [3,4]. The reason for this discrepancy may be related to the use of an elderly cirrhotic group in one of the studies [3] and the failure of the current Simcyp Cirrhosis Library to capture the full extent of the effects of cirrhosis in such patients. Nevertheless, this evaluation provides evidence in support of using prior demographic, physiological and ADME information to optimize the design of PK studies in patients with cirrhosis of the liver, as recommended by a recent EMEA Guideline [5].

REFERENCES

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