

A BOTTOM UP APPROACH TO PREDICTING THE PHARMACOKINETICS (PK) OF THEOPHYLLINE (THEO) AND ITS INTERACTION WITH FLUVOXAMINE (FLUV) IN LIVER CIRRHOSIS



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Introduction

Impaired hepatic function may have a major impact on drug PK and the magnitude of drug-drug interactions. Drug metabolizing enzymes appear to be differentially affected by the severity of liver cirrhosis; CYP1A2 and CYP2E1 activities are reduced by 40% and 20%, respectively, in mild (Child-Pugh class A) disease. As the relative contribution of a particular enzyme to the overall clearance of a drug may change with respect to Child-Pugh (CP) score, susceptibility to interaction with an inhibitor may also change. The objectives of this study were to use disease specific physiologically based PK models to predict the concentration-time profiles of THEO in healthy volunteers (HV), CP-A and CP-C subjects with and without concomitant administration of the potent CYP1A2 inhibitor FLUV.

Methods

Information on demographics and changes in the blood flow to different organs, CYP enzymes, liver size, protein binding, renal function, tissue composition, blood volume, organ size and gastric emptying has been incorporated into 3 separate population models within the Simcyp simulator (V10), corresponding to cirrhosis CP scores A (mild), B (moderate) and C (severe). Simulated studies were matched as closely as possible to the clinical study² for demographics and dosing schedule. Predicted clearance, concentration-time profiles, C_{max} and fold interaction values in HV, CP-A and CP-C populations were compared with observed values.

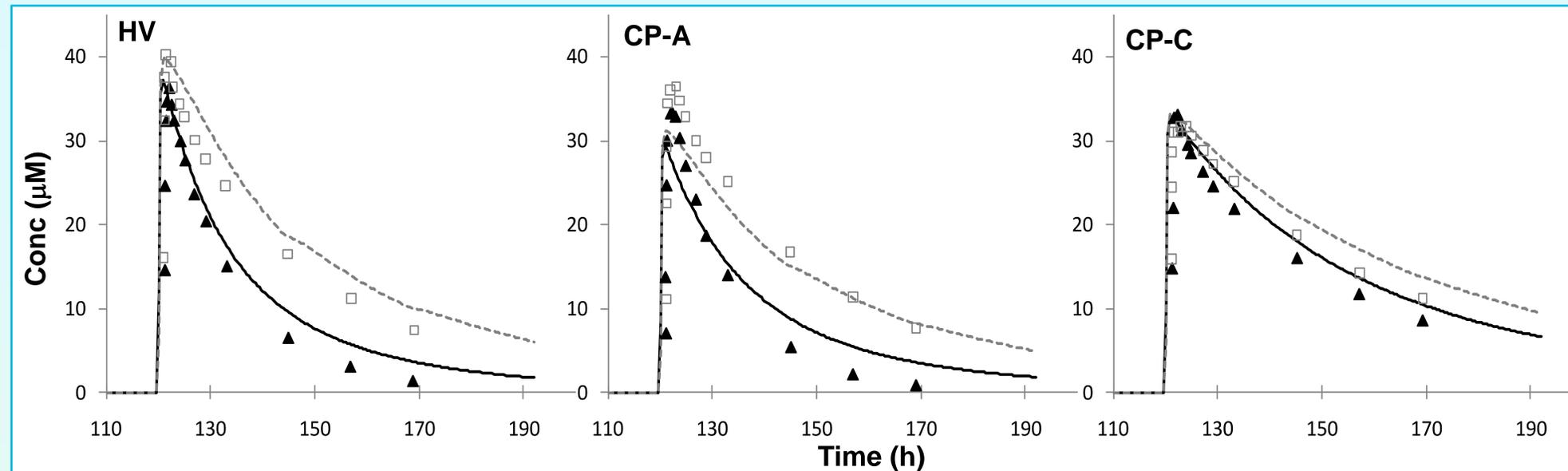


Figure 1. Mean predicted concentration-time profile of THEO in the absence (solid black line) and presence of FLUV (dashed grey line) in healthy volunteers (HV), Child-Pugh A (CP-A) and Child-Pugh C (CP-C). Observed data with and without interaction are shown by the grey open squares and closed black triangles respectively

Results

Concentration-time profiles of THEO with and without FLUV are shown in Figure 1. Overall changes in THEO PK are summarized in Table 1. Increasing severity of liver cirrhosis was associated with a 3-fold decrease in the oral

clearance (CL/F) of THEO and a reduction in the magnitude of interaction with FLUV.

Conclusions

Predicted changes in THEO PK were reasonably consistent with observed data (fold ratios ranged from 0.65 to 1.7). Oral clearance was markedly decreased in CP-C compared to HV and CP-A groups. The decreased metabolic clearance by CYP1A2 and relative increase in renal elimination in CP-C subjects resulted in a predicted fold-interaction that was lower than that obtained for HV, which was in agreement with the clinical study. Prior knowledge from a PBPK approach may be useful in guiding the conduct of clinical studies especially in populations such as those with liver cirrhosis.

Table 1. Summary of PK parameters for THEO in HV and CP-A & C and the fold interaction with FLUV

Population	PK Parameter	Observed ±SD	Predicted ±SD	Fold ratio (pred / Obs)
Healthy volunteer	CL/F (L.h)*	3.64 ± 0.6	3.06 ± 1.8	1.2
	C _{max} (µM)	38 ± 6	35 ± 11	1.1
	Fold Interaction**	2.7 ± 0.6	2.3 ± 0.9	1.3***
Child-Pugh A	CL/F (L.h)*	3.04 ± 0.8	2.0 ± 1	1.5
	C _{max} (µM)	42 ± 6	36 ± 11	1.2
	Fold Interaction**	2.1 ± 0.7	2.1 ± 0.7	1***
Child-Pugh C	CL/F (L.h)*	1.2 ± 0.4	0.7 ± 0.3	1.7
	C _{max} (µM)	36 ± 7	38 ± 12	0.94
	Fold Interaction**	1.13 ± 0.6	1.2 ± 0.3	0.65***

*From dose/AUC, **AUC ratio *** (Obs-1/Pred-1)

References

- Johnson et al, Clin Pharmacokinet 2010; 49: 189 – 206.
- Orlando et al, Clin Pharmacol Ther 2006; 79: 489 – 499.