

PBPK modeling based clinical dose adaptation in liver cirrhosis patients for seven CYP and UGT enzyme substrates

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In patients with **impaired liver function**, understanding the **pharmacokinetics** (PK) is crucial for effective and safe medication management. **Liver cirrhosis results in multiple physiological changes** mainly due to liver dysfunction and portal hypertension, and can significantly alter drug systemic clearance and exposure, posing challenges for appropriate dosing strategies [1-3]. **Determining appropriate dosing** for liver cirrhosis is complex due to the absence of a single reliable marker [1]. In this scenario, **physiologically-based pharmacokinetic (PBPK)** modeling emerges as a powerful tool, harnessing its ability to integrate mechanistic insights into the combination of pathophysiological changes and pharmacological properties of the drugs. This integration enables anticipation of the impact of liver cirrhosis, aiding in clinical dosage adjustments [4].

The present project aims to assess the predictive capability of PBPK-based simulations for the effects of liver cirrhosis on the metabolism of various substrates of cytochrome P450 (CYP) and uridine 5'-diphospho-glucuronosyltransferase (UGT) enzymes. Additionally, the project will propose strategies for utilizing PBPK-based simulations to suggest dose adjustments tailored to cirrhotic patients.

METHOD

5 test compounds administrated as a cocktail:

Clinical study conducted by Duthaler et al. [5], where 12 control patients and 36 patients with different Child-Pugh (CP) stages of liver cirrhosis were orally administered single doses of: efavirenz (50 mg), flurbiprofen (12.5 mg), omeprazole (10 mg), metoprolol (12.5 mg) and midazolam (2 mg). Blood samples were obtained until 24 hours after administration.

PBPK modeling workflow

PBPK model building in control patients

PBPK models were developed in Simcyp™

PK profiles predicted

Verification of predictions with control data

Parameter optimization

Extrapolation to liver cirrhotic populations

$$\frac{AUC_{control}}{AUC_{cirrhosis}} = \text{Correction factor}$$

$$\text{Correction factor} * \text{Dose} = \text{Corrected Dose}$$

	Efavirenz	Flurbiprofen	Omeprazole	Metoprolol	Midazolam
Dose (mg)	50	12.5	10	12.5	2
Cl (L/h)	11.4	1.49	24.1	138	45.0
F (fraction)	0.50	0.95	0.50	0.50	0.30
Cl/F (L/h)	22.70	1.57	48.10	275.00	150.00
Q ₀ (fraction)	0.99	0.99	0.99	0.95	0.99
Enzymes involved	CYP1A2/2B6/3A	CYP2C9	CYP2C19/3A	CYP2B6/2C9/2D6/3A	CYP3A4/3A5 UGT1A4

Drug Label recommendations in hepatic impaired patients

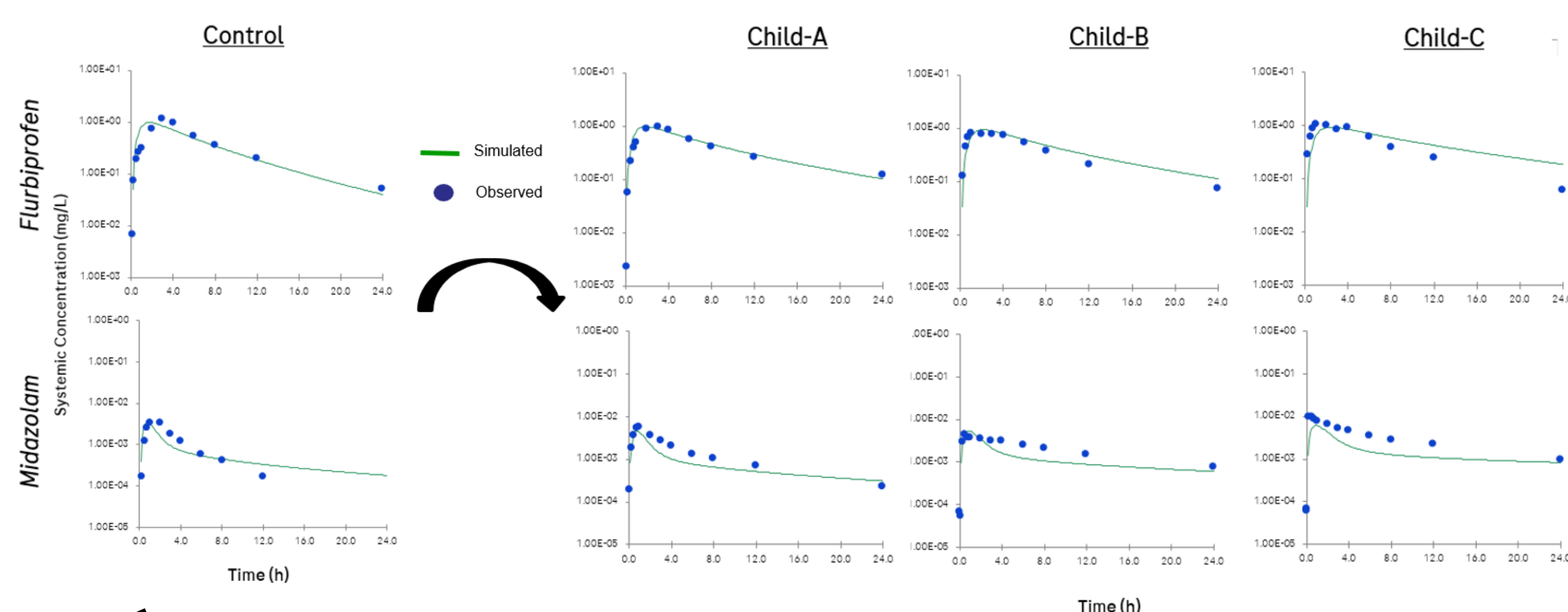
Flurbiprofen: not recommended for severe HI patients
Metoprolol: dose adaptation in HI is considered as not necessary (except in very advanced hepatic disease)
Omeprazole: dose should be adapted in severe HI patients if the treatment is for a long period
Midazolam: dose can be reduced in HI depending on the desired sedation effect
Efavirenz: mild HI patients can take the normal dose, but the dose should be reduced in severe HI patients

RESULTS

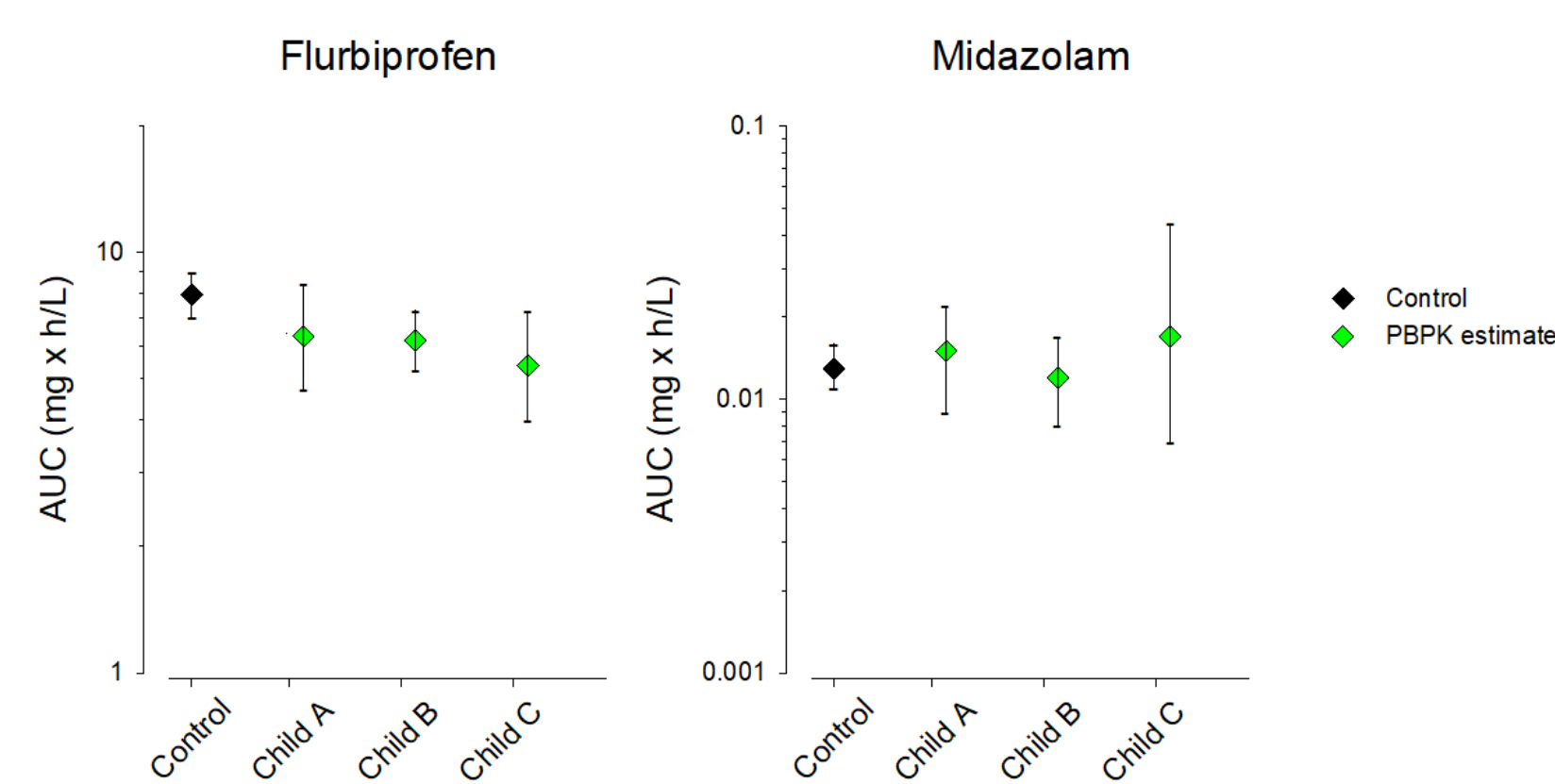
PBPK Simulated VS Observed plasma concentrations

Fit to data in healthy volunteers

Extrapolation to patients with liver cirrhosis



AUCs re-calculated with corrected dose



PBPK models were successfully able to predict the PK profiles of all 5 compounds with more than 80% of observed concentration points within 5th-95th percentiles of predictions.

Similarly, predicted AUC were within two-fold of observed values, except for omeprazolol AUC, which was overpredicted in mild cirrhotic patients, and flurbiprofen AUC, which was underestimated in severe cirrhotic patients.

For the 5 compounds of the Basel Cocktail, AUCs predicted with the adjusted doses in patients with liver cirrhosis resulted in AUCs comparable to those measured in control subjects.

PBPK based dose recommendations in hepatic impaired patients*

/*These dose adjustments are theoretical and should not be applied in clinical scenario without further investigations

Flurbiprofen: reduction of the dose by 2-fold (severe)
Metoprolol: reduction of the dose by, 3-fold (moderate) and 5-fold (severe)
Omeprazole: reduction of the dose by 3-fold (moderate) and 6-fold (severe)
Midazolam: reduction of the dose by 2-fold (mild), 3-fold (moderate) and 5-fold (severe)
Efavirenz: no dose adaptation seems to be needed

CONCLUSION

This study unveils findings from a clinical trial involving the administration of 6 compounds to both control subjects and individuals with liver cirrhosis. PBPK-based simulations were utilized to predict alterations in drug exposure resulting from pathophysiological alterations induced by liver cirrhosis. We confirmed the capacity of PBPK modeling to accurately capture exposure changes attributable to liver cirrhosis. Furthermore, predicted AUC were used to propose a dose adjustment and improve the clinical efficiency of efavirenz, flurbiprofen, omeprazole, metoprolol, and midazolam simulations.

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