TOWARDS QUANTITATIVE PREDICTION OF DISEASE-DRUG INTERACTIONS USING A PHYSIOLOGICALLY BASED PHARMACOKINETIC MODELLING APPROACH: SUPPRESSION OF CYP1A2 BY IL-6

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BACKGROUND

- It is known that circulating levels of pro-inflammatory cytokines (e.g. Interleukin [IL]-6) are elevated in patients with heart failure (1, 2). Elevated levels of cytokines can down-regulate expression and suppress activity of cytochrome P450 enzymes (CYPs) (3), with potential consequences for decrease in first-pass metabolism and clearance of co-administered small molecule drugs (SMD), thereby, lead to disease–drug interactions (4).
- Clinical studies have indicated a decrease in CYP 1A2 activity in congestive heart failure (CHF) patients (5,6) and an inverse relationship between cytokine levels and CYP activity was observed (5). Furthermore, exposure of hepatocytes to IL-6 *in vitro* leads to decreased expression/activity of CYP 1A2 (7).
- Although the clinical impact of disease-drug interactions mediated *via* suppression of CYPs has been modest (~ 2-fold change in victim drug exposure) (8), providing information on potential impact of cytokines or cytokine modulators on the disposition of SMDs could be very useful during drug development.
- While the understanding of *in vitro-in vivo* translation of cytokine suppression is still emerging (9), modelling and simulation approaches have the potential to successfully predict these disease–drug interactions.

OBJECTIVES

The aim of this study was to investigate the ability of an *In Vitro-In Vivo* extrapolation (IVIVE) linked PBPK model to predict the impact of elevated systemic IL-6 levels on the disposition of two CYP 1A2 substrates (caffeine and theophylline) in patients with CHF (5,6). Two independent clinical case studies have been simulated, and the impact of inter-donor variability in the *in vitro* data on the predicted outcome was also investigated.

METHODS

The Simcyp Population-Based Simulator (version 14.1, Sheffield, UK) was used to simulate the time course of "victim" drugs (caffeine or theophylline) and "perpetrator" (IL-6) concentrations in plasma. Plasma concentration-time profiles of paraxanthine was also simulated to calculate the caffeine metabolic ratio (paraxanthine/caffeine concentration ratio). Study design, dosage regimen and characteristics of the virtual subjects were matched closely to participants of the clinical studies (5, 6) in terms of numbers, age, and sex. The PBPK model included a semi-mechanistic suppression model (Eq.1) (9) that combined *in vitro* suppression data with a range of systemic steady-state levels of IL-6 (1 to 1000 pg/mL) to quantitatively predict the disease-drug interaction *via* IL-6 mediated suppression of CYP 1A2. The enzyme suppression model makes the assumption that the time-dependent concentration of IL-6 (I_t) affects the rate of enzyme synthesis in the liver directly.

$$\frac{dEnz_{act,H-1A2}}{dt} = k_{deg,H-1A2} \cdot Enz_{0,H-1A2} \cdot \left[1 + \frac{(E_{min} - 1) \times [I]_t}{EC_{50} + [I]_t}\right] - k_{deg,H-1A2} \cdot Enz_{act,H-1A2(t)} \quad \text{Eq. 1}$$

$Enz_{act,H-1A2}(t)$ is the amount of active CYP1A2 at any given time in the liver; $Enz_{0,H-1A2}$ is the basal amount of CYP1A2 in the liver ($Enz_{act,H-1A2(t)} = E_0$ at t= 0). E_{min} is the minimum CYP enzyme activity *in vitro* in hepatocytes (i.e., maximum suppression) expressed as a fraction of vehicle control. EC_{50} is the concentration that supports half - (E_{min} -1)(i.e., half of the maximum suppressive effect); $[I]_t$ is the perpetrator (IL-6) concentration at time t. Mean degradation rate constant (k_{deg}= 0.0183 1/h) value for hepatic CYP 1A2. The mean values of E_{min} (0.16) and EC_{50} (546 pg/mL) were taken directly from the *in vitro* data reported by Dickmann *et al*. (7).

RESULTS

Case study 1: Impact of IL-6 on the elimination of caffeine in CHF patients

There was decrease in caffeine clearance by CYP1A2 in the presence of increasing concentrations of IL-6 (up to 1000 pg/mL) in virtual subjects. At 500 pg/mL of IL-6, the predicted median caffeine metabolic ratio (surrogate for CYP1A2 activity) was comparable with the observed data (5) (0.33 vs. 0.36) (Table 1).

Table 1 : Predicted and observed CYP 1A2 activity (caffeine metabolic ratio) in CHF patients

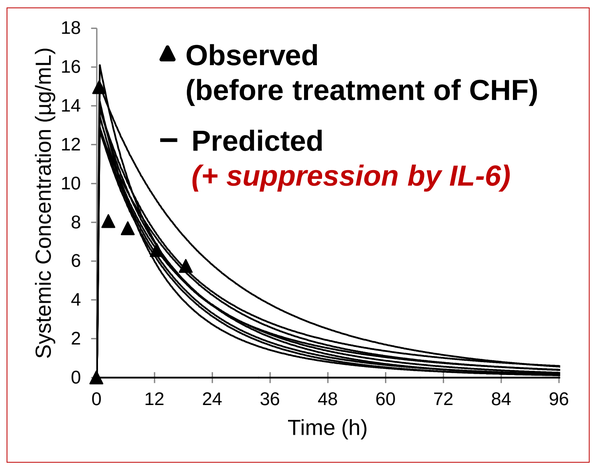
	Caffeine Metabolic Ratio Median (range)
Predicted	0.33 (0.24-0.44)
Observed (5)	0.36 (0.04-1.14)

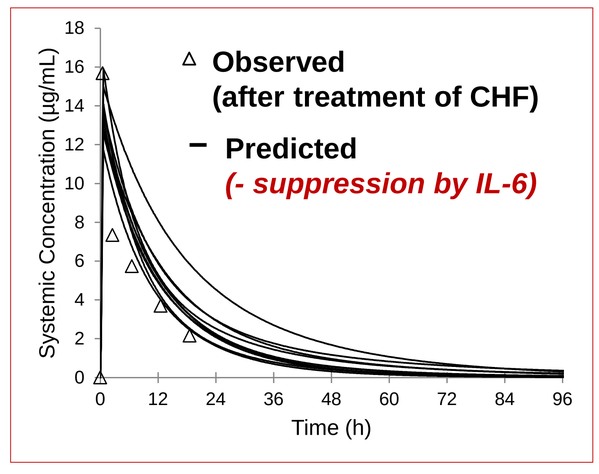
Case study 2: Impact of IL-6 on the elimination of theophylline in CHF patients

- Predicted and observed data showing the effect of steady-state levels of IL-6 (@ 500 pg/mL) on the clearance and plasma pharmacokinetics of theophylline in CHF patients (before and after treatment of congestive heart failure) are shown in Table 2 and Figures 1 & 2, respectively.
- Using the mean *in vitro* suppression data for CYP 1A2 activity, at 500 pg/mL levels of IL-6, predicted decrease in systemic clearance (7-50%) (Table 2) comparable with the observed clinical data (25-69%) (6). The simulated systemic plasma concentration profiles of theophylline (Figure 1) were also similar to observed concentrations.
- Simulations using concentrations of 1, 5, and 10 pg/mL IL-6 (the baseline levels reported in healthy volunteers) (1) showed minimal change in theophylline pharmacokinetics to levels in the absence of IL-6 and the predicted exposure was comparable with the observed data (Figure 2) following treatment of CHF.

Table 2 : Predicted and observed theophylline clearance in patients before and after treatment of CHF.

Theophylline Total Clearance (mean ± s.d.)(mL/h/kg)			
	Before treatment of CHF *(+ suppression)*	After treatment of CHF *(- suppression)*	Decrease in clearance (range)
Predicted	**27.3 ± 13.3**	**38.4 ± 19.4**	**7%-50%**
Observed (6)	**21.7 ± 7.9**	**43.4 ± 13.2**	**25%-69%**





Figures 1-2: Predicted and observed theophylline systemic concentration-time profiles in patients before (Fig 1 – left panel) and after treatment of CHF (Fig 2 – right panel).

Case study 3: Impact of inter-donor variability in the in vitro data on the predicted outcome

Significant inter-donor variability was observed in the *in vitro* suppression data for CYP 1A2 (5), EC_{50} and E_{min} values ranging from 142 to 1050 pg/ml and 0.06 to 0.24, respectively. Sensitivity analysis indicated a decrease in theophylline total clearance in the presence of IL-6 (@ 500 pg/mL; within the range of observed IL-6 levels in CHF patients) ranging from 17% to 56% when accounting for inter-donor variability in the *in vitro* E_{min} and EC_{50} data (Figure 3).

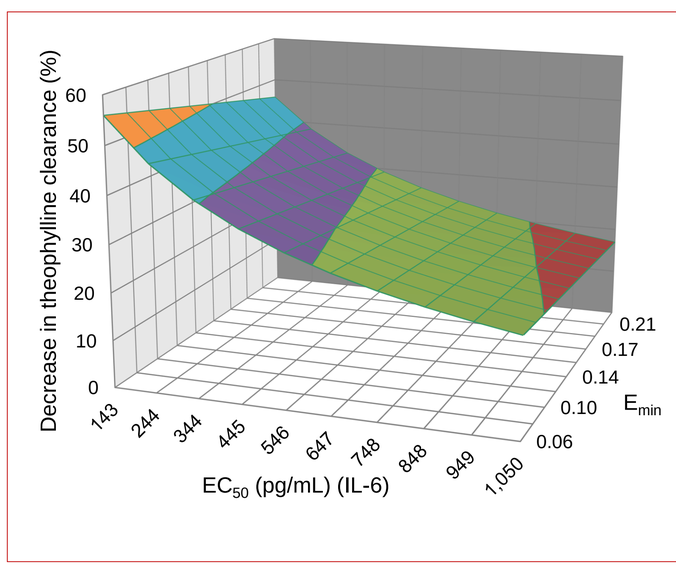


Fig 3: Impact of observed inter-donor variability in the IL-6 induced in vitro suppression of CYP1A2 activity (E_{min} & EC_{50}) in hepatocytes on the predicted total clearance of theophylline in virtual CHF patients.

CONCLUSIONS

- Methods to quantitatively predict the effects of cytokines on CYP isozymes are still emerging.
- Adapting an IVIVE-PBPK approach previously used to model the effect of IL-6 on CYP3A4 expression levels (9) resulted in a model that could capture changes in CYP1A2 expression following exposure to IL-6, and was reasonable to predict the observed change in caffeine and theophylline pharmacokinetics in patients with congestive heart failure.
- Whilst these results are encouraging the impact of other potential contributing factors such as high variability in circulating levels of IL-6 in CHF patients, significant inter-donor variability in the *in vitro* data and the role of cytokines other than IL-6 warrant further investigation.

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