Sources of inter-individual variability in IVIVE of clearance. An investigation into the prediction of benzodiazepine clearance using a mechanistic population-based pharmacokinetic model

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BACKGROUND Accurate **prediction of *in vivo* clearance** is required for understanding **drug efficacy and toxicity** during drug development. **Howgate *et al* (2006)** successfully predicted *in vivo* clearance for 25 drugs, in contrast to other studies noting **an under-prediction trend** (Houston *et al*, 1997; Obach *et al*, 1997 and 1999; Hallifax *et al*, 2010). Traditionally, methods involve human liver microsomal (**HLM**) or hepatocyte (**HHEP**) data, using **'average human'** scaling factors and comparing to **one clinical study**. However, **CYP3A** substrates have **large inter-individual variability** of *in vivo* clearance (Galetin *et al*, 2004; Rawden *et al*, 2005). Assessment of inter-individual variability of *in vivo* clearance allows analysis of **range** and identification of individuals with **extreme clearance values.**

STUDY AIMS Evaluation of:

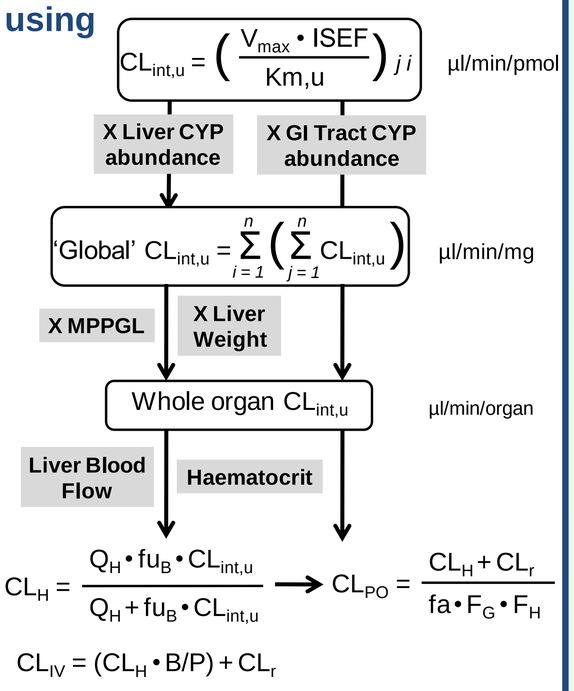
1) **Clearance prediction accuracy** for alprazolam, triazolam and midazolam

2) Impact of **variable IVIVE parameters** on variability of predicted *in vivo* CL

3) **Variability in CYP3A enzyme abundance**: Separation of inter-individual from experimental variability

METHODS 1) **Bottom-up**: IVIVE of *in vitro* intrinsic clearance (CL_{int}) and **Top-down**: Back-calculation from *in vivo* intravenous clearance (CL_{iv})

Figure 1. Incorporation of population-specific variability into predicted *in vivo* clearance using *in vitro* recombinant CYP (rhCYP) data



Grey boxes: Incorporation of variability
ISEF = Inter-System Extrapolation Factor (Proctor *et al*, 2004 and Crewe *et al*, in press)
i = no. of metabolic pathways
j = no. of CYP isoforms

2) **Simulations (Simcyp V10):** Trial design mimicked clinical studies. Comparison to 10 randomly selected studies for each drug and both CL_{iv} & CL_{po} (except alprazolam and triazolam CL_{iv}: only 4 studies available). Dataset of >150 studies. Variability inputs (% CV) were removed for parameters in turn **(CYP3A4 liver/gut abundance, MPPGL, liver volume, haematocrit)**. Impact on variability of CL_{iv} and CL_{po} was assessed.

3) Separation of inter-individual from experimental variability in CYP3A4 abundance using repeat measurement ELISA protocol in individual HLM (n=52).

RESULTS **1) Clearance prediction accuracy**

Bottom-up: Predicted clearances were within 2-fold of observed for triazolam and midazolam but 2 to 3.7-fold higher than observed for alprazolam.
Top-down: *In vivo* CL_{int} allowed more accurate assessment of variability of *in vivo* clearance when predictions were optimal (within 2-fold) (Figure 2).

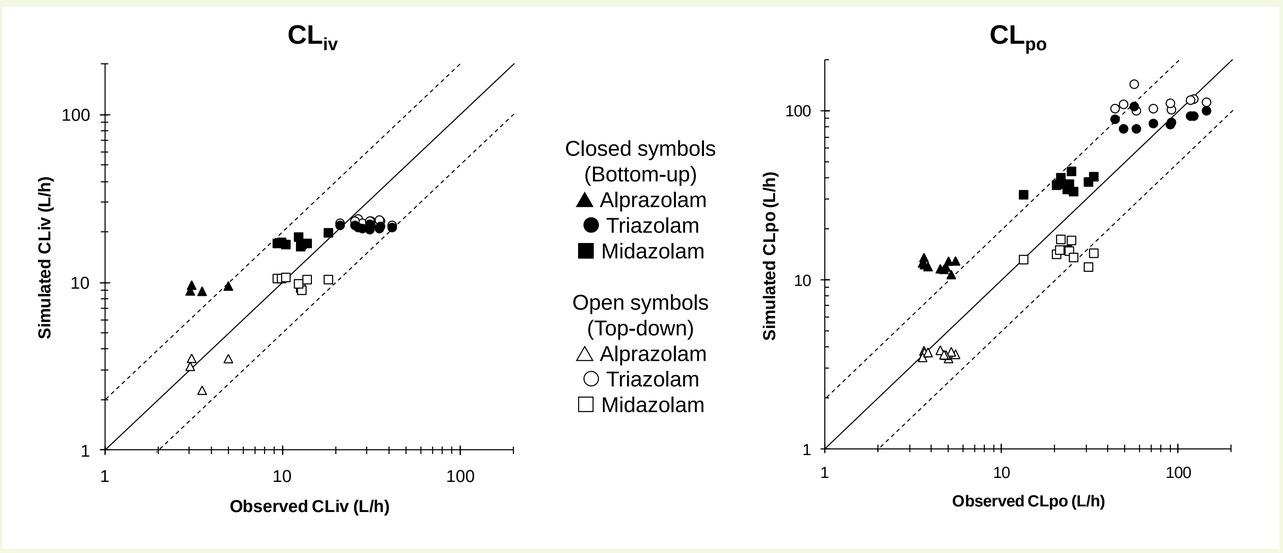


Figure 2. Accuracy of simulated CL_{iv} and CL_{po}. Bottom-up vs Top-down
Solid line: unity. Dotted lines: 2-fold error. Data points are geometric mean

2) Impact of parameter CV on variability in predicted triazolam CL

The IVIVE parameters with the greatest impact on variability of predicted *in vivo* clearance were **hepatic CYP3A4 abundance** and **MPPGL.**
As CV values for these parameters were increased from **0-100**% in turn, variability of **predicted *in vivo* clearance** increased by **230%** (both CL_{iv} and CL_{po}; hepatic CYP3A4 abundance) and **39%** and **62%** (CL_{iv} and CL_{po}, respectively; MPPGL).

3) Separation of inter-individual from experimental variability for hepatic CYP3A4 abundance

CV for hepatic CYP3A4 abundance from **literature meta-analysis** was **95%.**
CV for hepatic CYP3A4 abundance from **experimental data** (representing '**true' inter-individual variability -** repeat measurement ELISA protocol) was **41%.**

Large variability in observed clearance was seen between different clinical studies. Mean CL_{iv}: Ranged 1.4, 1.8 and 2-fold for alprazolam, triazolam and midazolam, respectively.
Mean CLpo: Ranged 1.5, 2.5 and 3.3-fold, respectively.

Variability of predicted *in vivo* clearance was initially over-estimated by 1.8 to 3.6-fold. Use of a **reduced hepatic CYP3A4 CV of 41%** (representative of inter-individual variability alone), improved predictions of variability in clearance for all drugs to within 2-fold of observed (Figure 3).

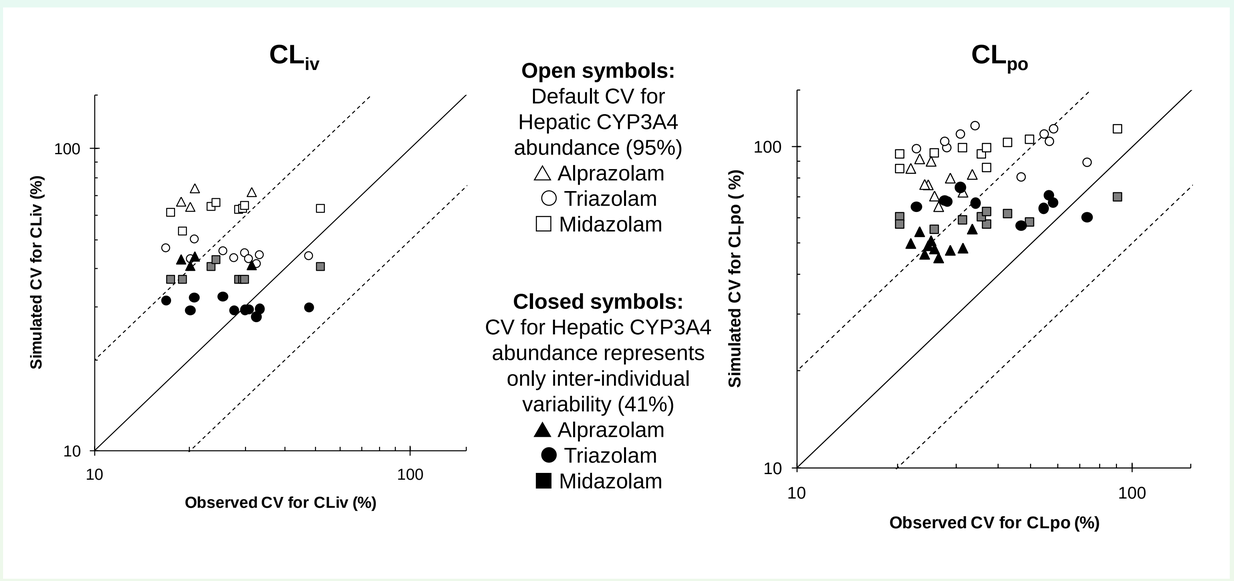


Figure 3. Impact of 'true' inter-individual variability CV (41%) for liver CYP3A4 abundance on variability of CL_{iv} and CL_{po}
Solid line: unity. Dotted lines: 2-fold error. Data points are geometric mean

CONCLUSIONS

- *In vitro* rhCYP data can be used to accurately predict *in vivo* clearance for a range of different clinical studies (seen here for triazolam and midazolam).
- Different clinical studies show significant variability of *in vivo* clearance.
- A lack of incorporation of variability in both *in vitro* and *in vivo* data could contribute to inconsistent accuracy of clearance predictions (Houston *et al*, 1997; Obach *et al*, 1997 and 1999; Howgate *et al*, 2006; Hallifax *et al*, 2010).
- There is a need for refinement of reported values of variability for IVIVE parameters (to distinguish experimental and inter-individual variability).
- Reduction of variability in hepatic CYP3A4 abundance to a value representing only inter-individual variability (CV 41%) would seem the best approach for estimation of variability of CYP3A4 *in vivo* clearance using *in vitro* elimination data.

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Study accepted for publication. Available 'Early Online': http://informahealthcare.com/xen