Modelling Toxicodynamic Feedback is Critical in Recovering Toxicokinetics in Acetaminophen Overdose

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Abstract

The hepatotoxicity of acetaminophen (APAP) has been extensively studied and modelled. However, many reported models fail to take in to account the depletion of key metabolic cofactors in response to high doses of APAP and the resulting impact on enzyme-mediated clearance and pharmacokinetics of APAP and its metabolites.

Models should account for the heterogenous expression of drug metabolising enzymes (DMEs) across the liver lobule, to recover higher perivenal CYP-mediated xenobiotic metabolism, leading to higher concentrations of reactive oxygen species (ROS) in these regions. Higher concentrations of ROS lead to activation of NRF2 (a transcription factor that protects against oxidative damage), and increasing turnover of anti-oxidant species as a protective mechanism against hepatotoxicity. We present a model incorporating real time scaling of clearances based on co-factor availability, zonation of DMEs, and NRF2 regulated turnover of the protective anti-oxidant glutathione.

Background

The putative mechanism mediating observed toxicity in APAP overdose is driven by saturation of the main sulfotransferase (SULT) clearance pathways, due to the depletion of the 3'-Phosphoadenosine-5'-phosphosulfate (PAPS) co-factor.

The fraction of the dose metabolized through CYP450 mediated clearance pathways is subsequently increased, relative to therapeutic doses, resulting in excessive formation of the reactive metabolite N-acetyl-p-benzoquinone imine (NAPQI). While the lower amounts of NAPQI produced at therapeutic levels can be eliminated through conjugation with reduced glutathione (GSH), overdose results in a depletion of GSH, formation of protein adducts, and oxidative stress.

As a result of conjugation with NAPQI, GSH concentrations in the hepatocyte decrease. In response to high levels of ROS, free NRF2 concentrations increase, subsequently upregulating both the basal synthesis rates of GSH as well as increasing the rate of reduction from it's oxidized form, GSSG. This response reduces the impact that high doses of APAP has on GSH levels and reduces free reactive metabolite concentration in the liver.

Methods

We present a physiologically based toxicokinetic model (PBTK) model incorporating the critical co-factor dependence of SULT mediated metabolic clearance, GSH depletion, regional drug metabolism, and feedback of NRF2-mediated upregulation of basal turnover of GSH, as well as the rate of reduction of oxidized glutathione (GSSG) to GSH. Therapeutic (1000mg oral) and overdose (20000mg oral) scenarios were simulated to compare the dynamics of the model at low and high doses.

We have implemented a 6-compartment liver model, incorporating hepatic zonation of drug metabolizing enzymes, increasing CYP-mediated metabolism in the perivenal region of the liver lobule. Toxicodynamic models describe the depletion of key co-factors and the resulting feedback on toxicokinetic parameters.

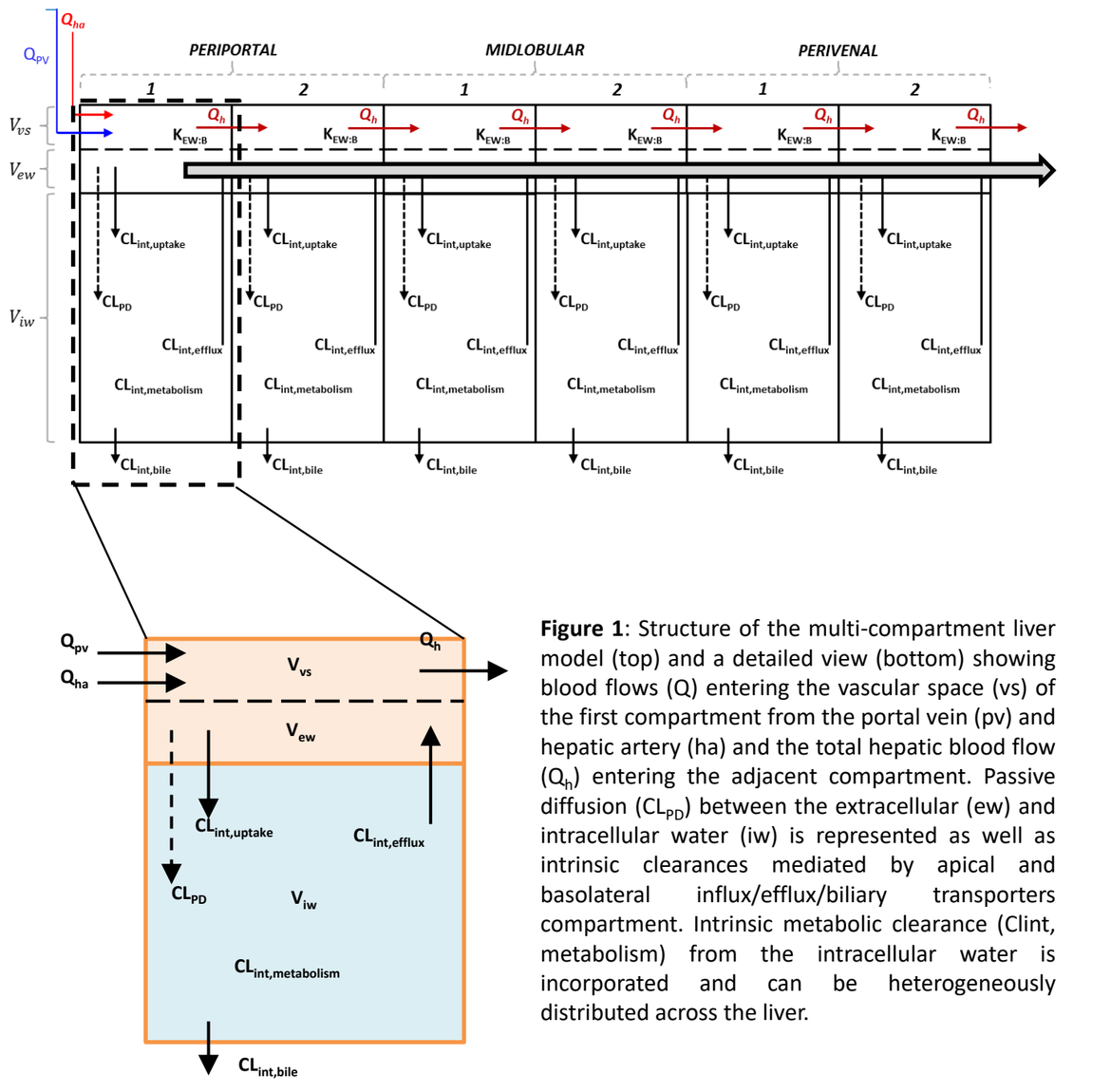
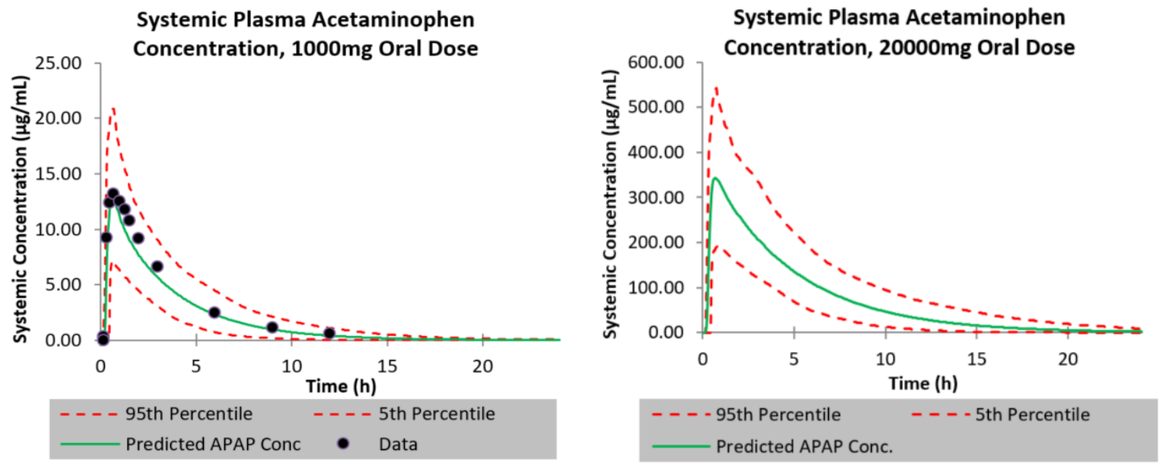
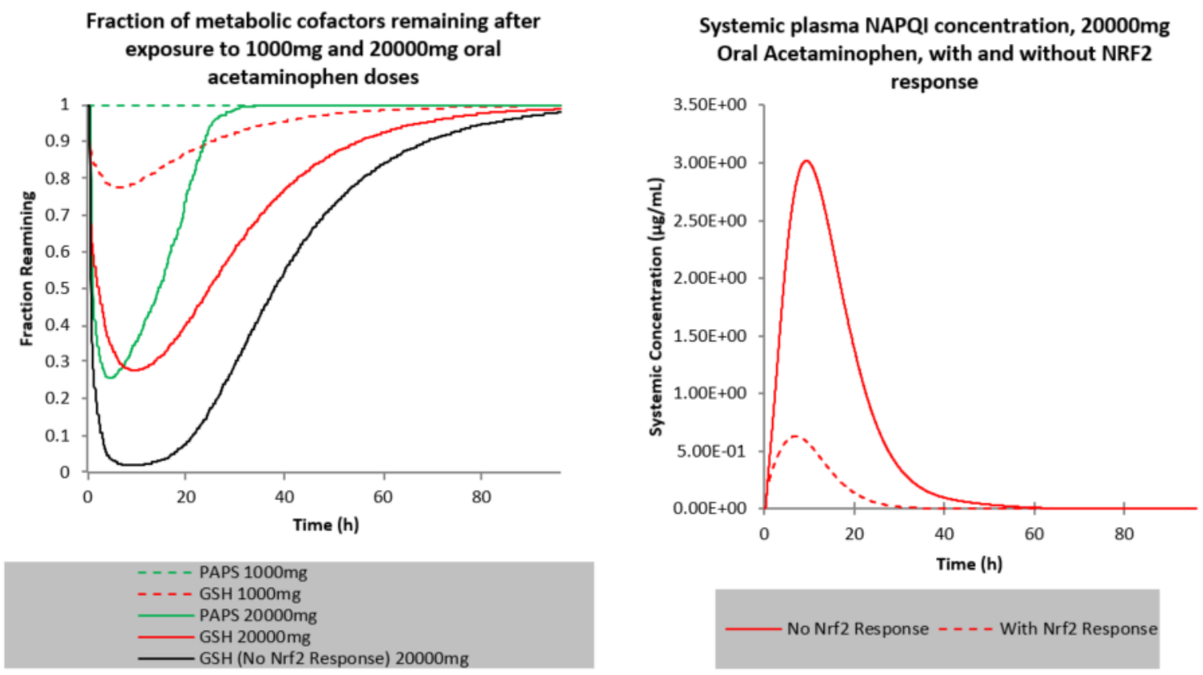


Figure 1: Structure of the multi-compartment liver model (top) and a detailed view (bottom) showing blood flows (Q) entering the vascular space (vs) of the first compartment from the portal vein (pv) and hepatic artery (ha) and the total hepatic blood flow (Q_h) entering the adjacent compartment. Passive diffusion (CL_{PD}) between the extracellular (ew) and intracellular water (iw) is represented as well as intrinsic clearances mediated by apical and basolateral influx/efflux/biliary transporters compartment. Intrinsic metabolic clearance (Clint, metabolism) from the intracellular water is incorporated and can be heterogeneously distributed across the liver.

Results

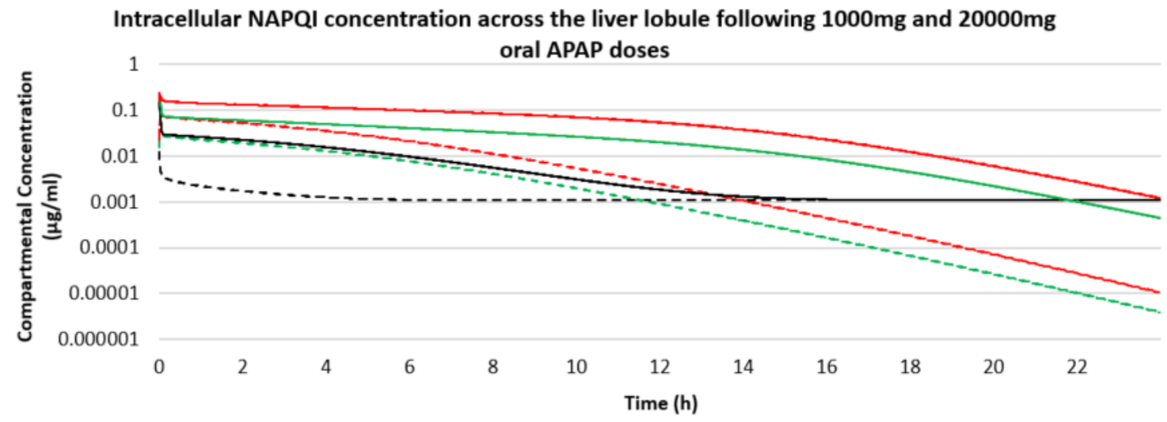


Figures 2 & 3: Simulations of therapeutic (left) and overdose (right) pharmacokinetics using a permeability-limited liver model. Observed data from Tanner *et al* [1]



Figures 4 & 5: Simulations of PAPS and GSH cofactor depletion (left) and plasma NAPQI concentrations (right), in response to therapeutic and overdose cases, with and without Nrf2 response in the permeability limited model

Figure 6: Simulations of intracellular concentrations in the periportal (black), midlobular (green) and perivenal (red) regions of the liver in response to therapeutic (dashed) and overdose (solid) doses using the multi-compartment liver model.



Conclusions

- Our model reproduces *in vivo* time-course data of acetaminophen plasma concentrations in the therapeutic dosing regimen using a permeability-limited liver model
- The model captures the depletion of metabolic cofactors in response to supra-therapeutic doses, which feedback on the clearance of APAP via these metabolic pathways
- The NRF2 and glutathione redox system is modelled and, in response to increased reactive oxygen species, GSH synthesis is upregulated, resulting in reduced depletion of GSH and so reduced peak NAPQI concentrations
- Higher NAPQI concentrations result in greater hepatotoxicity, and so the modelled NRF2-regulated response demonstates a protective mechanism against DILI
- Using the multi-compartment liver model we predict the effects of heterogeneity of drug-metabolising enzymes. We see greater NAPQI concentrations in the perivenal zone, consistent with *in vivo* findings that the most acute and extensive cell damage following overdose is observed in the perivenal region

References

[1] Tanner, Trevor et al. "The Pharmacokinetic Profile of a Novel Fixed-Dose Combination Tablet of Ibuprofen and Paracetamol." *BMC Clinical Pharmacology* 10 (2010): 10. *PMC*. Web. 23 Aug. 2018.

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