Development and assessment of a nested enterocyte-cytochrome P450 turnover model and implications for mechanism-based inhibition of gut wall metabolism

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Introduction

Prediction of drug-drug interactions (DDIs), e.g., mechanism-based inhibition (MBI), is an essential application in physiologically-based pharmacokinetic (PBPK) modelling, where small intestinal metabolism plays an important role.

PBPK modelling of MBI in the gut will depend on the level of active enzyme in the gut wall (A_{ent,GI}), a function of inhibitor concentration (\(k_{\text{deg,Ent}}\)). Its maximal rate of enzyme inactivation (\(k_{\text{deg,Ent}}\)), the inhibitor concentration producing half of the maximal rate of inactivation (\(k_{\text{deg,Ent}}\)), and the inhibitory concentration producing half of the maximal rate of inactivation (\(k_{\text{deg,Ent}}\)). Further, the level of interaction will be determined by the level of active enzyme at steady state (A_{ent,GI}) and enzyme degradation rate (\(k_{\text{deg,Ent}}\); Equation 1) [1-3].

\[
d\frac{dc_{\text{deg,Ent}}}{dt} = \frac{k_{\text{deg,Ent}}}{k_{\text{deg,Ent}} - c_{\text{deg,Ent}}} \left( k_{f,\text{syn,ent}} - k_{f,\text{deg,Ent}} - c_{\text{deg,Ent}} \right) \]

Where \(k_{\text{deg,Ent}}\) is a surrogate parameter of the combined turnover rate of the enterocyte and enzyme. Enzyme turnover determines the timeframe and extent of MBI, where some anecdotal evidence have indicated potential overestimations of inhibition of gut metabolism.

Aim and objectives

The aim was to theoretically examine the nesting and hierarchy of enterocyte and CYP3A4 enzyme turnover and its impact on MBI in the gut wall using a systems pharmacology approach and independent information on enterocyte turnover. This would be carried out through the development and assessment of a nested enzyme within-enterocyte turnover (NET) model coupled to a minimal PBPK model.

Methods

A nested enzyme turnover (NET) model describing CYP3A4 activity in the gut wall was developed in Matlab R2010a, allowing the simulation of enzyme turnover nested within the enterocyte subject to independent enterocyte turnover (Figure 1 and 2).

Realistic parameter estimates and ranges of \(k_{\text{deg,Ent}}\), the degradation rate of small intestinal CYP3A4 (k_{\text{deg,Ent}}), \(k_{\text{deg,Ent}}\) and \(k_{\text{deg,Ent}}\), where explored through a simulation based exploratory sensitivity analysis utilising the developed NET model.

Results (continued)

In general, the developed NET model was associated with a lower inhibition of small intestinal CYP3A4 activity following MBI as compared to the conventional PBPK modelling approach (k_{\text{deg,Ent}}=0 h^{-1}).

Comparing the outcome of the NET model on intestinal CYP3A4 activity using observed data of k_{\text{deg,Ent}} (0.01 h^{-1}) and k_{\text{deg,Ent}} (0.03 h^{-1}) as compared to the hybrid parameter k_{\text{deg,Ent}} (0.04 h^{-1}) in the conventional model, indicated the NET model to display a lower degree of inhibition for a number of MBIs.

The increase in intestinal CYP3A4 activity was further apparent for inhibitors for which overpredictions have been reported utilising a conventional modelling approach, including fluoxetine (K_{\text{u,Ent}}=5.19 µM, k_{\text{deg,Ent}}=0.02 h^{-1}) and mibefradil (K_{\text{u,Ent}}=2.23 µM, k_{\text{deg,Ent}}=24 h^{-1}), displaying approximately 1.13 and 1.31 fold higher activity of intestinal CYP3A4 respectively following MBI (Figure 5).

Discussion and Conclusions

The model displayed potential to improve on predictions of mechanism-based inhibition, producing a lower level of inhibition as compared to the conventional modelling approach.

The utilisation of a more physiological description of small intestinal enzyme and cell dynamics following DDIs has the potential for further application on a number of subpopulations and disease states where the enzyme or enterocyte turnover may be altered.

The developed NET model is, to our knowledge, the first PBPK model to consider the nesting and hierarchy of the enzyme and enterocyte turnover in the small intestine.

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References
