T1530-05-033

Assessing the Role of Intracellular Binding Protein in Drug-Induced Bile Acid Transporter Inhibition Using Quantitative Systems Pharmacology (QSP) Modeling

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PURPOSE

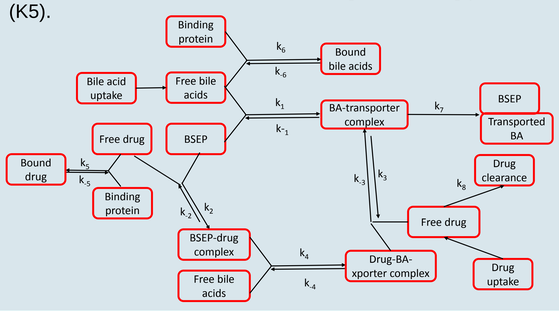
Bile acid transporter inhibition has been shown to be an important mechanism of drug-induced liver injury (DILI), but the biophase responsible for the transporter inhibition is unclear. While the free-drug hypothesis would suggest that only unbound drug can inhibit bile acid transporters, there has been success in predicting bile acid transporter inhibitor-mediated DILI with DILIsym (1,2), which uses total drug concentration to represent the transporter inhibition. The role of intracellular protein binding of bile acids is also unclear. The goal of the current simulation work was to investigate the impact of drug and bile acid binding kinetics on BSEP inhibition using a mechanistic QSP model.

OBJECTIVE

The objective of this research is to elucidate the effect on bile acid accumulation of the affinity between binding protein and both bile acids and drug when a bile salt transporter-inhibiting drug is present. The effect of binding protein concentration in the liver will also be considered.

METHOD

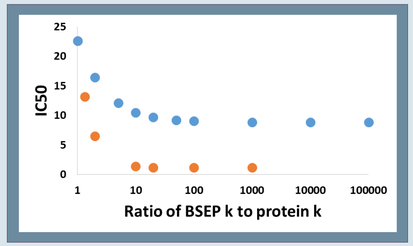
We constructed a QSP model of drug and bile acid interactions with both binding protein and the bile salt export pump (BSEP) in the hepatocyte. The model included protein binding of both drug and bile acid, and included both constant and dynamic drug and bile acid concentrations. A further modification including the potential for bile acid chaperoning (i.e. transport of bound bile acids) was also added (not shown in diagram). We then subjected the model to a sensitivity analysis around several parameters, including the rate constant between drug and BSEP (K2) and the rate constant between drug and binding protein (K5).



RESULTS

Static model:

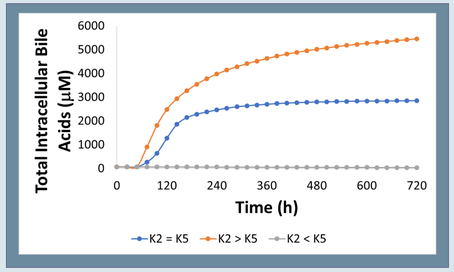
Increasing the affinity of the drug for BSEP compared to the binding protein decreases the apparent IC_{50} of the system and thus increases the potency of the inhibitor. The effect of increasing the drug-BSEP rate constant is different from the effect of decreasing the drug-binding protein rate constant even though the ratio of the rate constants remains the same.



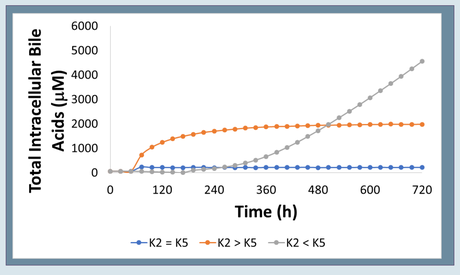
Apparent IC_{50} of the static system when the rate constant for drug binding with BSEP and the rate constant for drug binding with protein are varied. The nominal K_i was 1 in this case; as such, the case where the rate constants are equal reflects the free-drug hypothesis; as the relative affinity of the drug for BSEP over protein increases, it becomes a more potent inhibitor. Interestingly, this effect is more pronounced when the drug-protein constant is decreased (orange) than when the drug-BSEP constant is increased (blue).

Dynamic model:

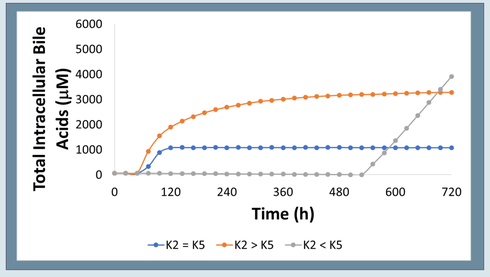
In the dynamic model, the drug-BSEP and drug-protein rate constants still matter. The total amount of binding protein matters as well, but when K_i is low, increases in the amount of binding protein available increase the bile acid accumulation in the system. This is possibly because the larger protein concentration captures more bile acids in the cell when transport out of the cell becomes more difficult.



Accumulation of bile acids when protein is available in excess for cases when drug affinity for binding protein is less than that of BSEP (orange), equal to that of BSEP (blue), and greater than that of BSEP (gray). For this simulation, K_i was set quite low, so inhibition effects are apparent when the affinities are equal. Accumulation is enhanced when drug has more affinity for BSEP, just as in the static model.



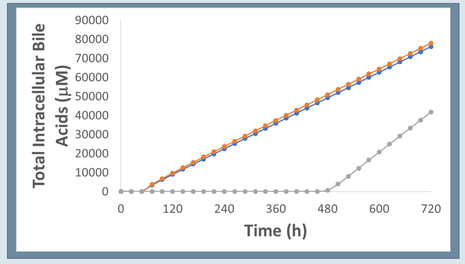
Accumulation of bile acids when protein is not available in excess; at right, protein concentration is 400 μM (near the physiological concentration of the main BA binding protein l-FABP), and at left, 100 μM. Interestingly, bile acid accumulation is much lower in both cases than in the high-protein case, suggesting that bile acids can use excess binding protein as a repository when BSEP is inhibited. Also, substantial increases in bile acids occur when drug has high affinity for binding protein, as the drug is saturating the binding protein.



K2: Affinity of drug to BSEP K5: Affinity of drug to binding protein

Chaperoning model:

When chaperoning, a hypothesis suggesting that BSEP-mediated bile acid transport is dependent upon the intracellular binding of BSEP, is represented in the model, bile acids accumulate more substantially than in the dynamic or static model. This suggests that the drug-protein interaction and the drug-BSEP interaction are both contributing to the bile acid accumulation.



Accumulation of bile acids in the chaperoning model when protein is available at physiological concentrations (400 μM). When chaperoning is active, the case in which affinity of the drug for BSEP is higher than that of protein (orange) and equal to that of protein (blue) are roughly equivalent. Accumulation in both cases is more pronounced than in the simple dynamic model.

CONCLUSIONS

1. Differences of drug affinity for BSEP and for binding protein can have a significant effect on bile acid accumulation. If the drug has a similar affinity for BSEP and for the binding protein, the free-drug hypothesis may accurately reflect the system; however, if these affinities are different, the free-drug hypothesis may underestimate the inhibition that is occurring.
2. The concentration of binding protein in the system was also shown to be an important consideration, as binding protein could plausibly act as a repository for bile acids and thus exacerbate bile acid accumulation.
3. Complex behavior such as chaperoning – the process by which binding protein facilitates the interaction between bile acids and transporters – may imply a role for bound drug in inhibiting bile acid transport and thus may render the free-drug hypothesis unable to describe the system adequately.
4. Experiments investigating the relative affinity of BSEP-inhibiting drugs for BSEP and intracellular binding proteins such as l-FABP could help elucidate the role of bile acid transporter inhibition in DILI.
5. Models of DILI may benefit from the explicit inclusion of protein binding behavior in the model in lieu of using the assumption of a fixed drug/bile acid fraction unbound.

ACKNOWLEDGEMENTS

The authors recognize the members of the DILI-sim Initiative, under whose auspices the DILIsym software was developed; Dr. Hugh Barton and the Protein Binding Focus Group within the DILI-sim Initiative were instrumental in the development of this research.

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