Mathematical Representation of Drug-Induced Crystal Nephropathy Using a Quantitative Systems Toxicology Approach

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PURPOSE

Drugs may cause crystal nephropathy by precipitating within kidney tubules or inducing the precipitation of endogenous compounds. A mechanistic mathematical model of drug-induced crystal nephropathy was developed within the context of RENAsym® v1A to help de-risk drug development programs by predicting the potential of a drug to cause crystal nephropathy. RENAsym® is a quantitative systems toxicology model of acute kidney injury that includes representation of proximal tubule cells, drug-induced cell death, and resultant biomarker responses. The crystal nephropathy model describes the formation, aggregation, distribution and elimination of crystals within the kidney and the subsequent toxic effects on kidney function.

OBJECTIVE

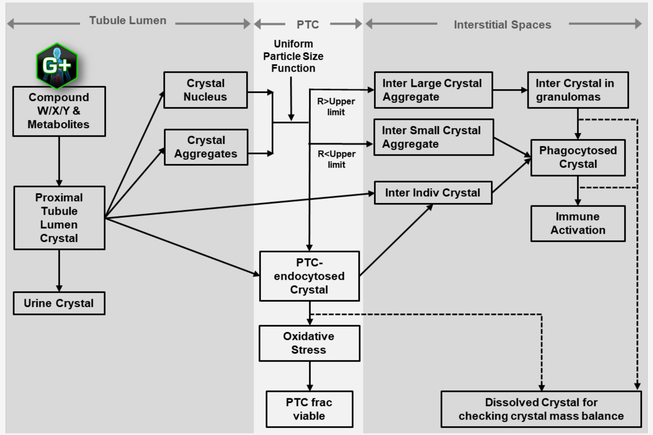
The crystal nephropathy model was developed using ethylene glycol-induced calcium oxalate crystal formation as an exemplar due to the amount of literature data available to inform model parameterization. Further development of the model to compounds such as indinavir was undertaken next.

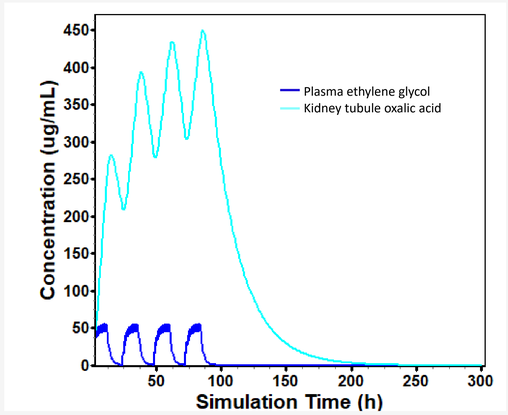
METHODS

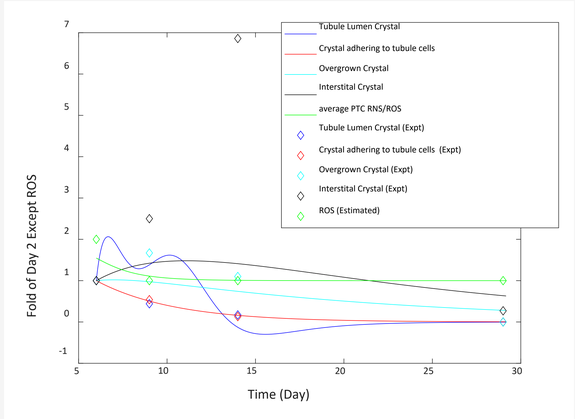
A PBPK model representing ethylene glycol and its metabolites glycolic acid, glyoxylic acid, and oxalic acid was constructed using GastroPlus® Version 9.8 to inform oxalate concentrations in the kidney tubule. Precipitation of calcium oxalate, crystal disposition, crystal uptake by tubular cells, cell death due to crystal induced oxidative stress, and crystal clearance was then parameterized using published data in mouse and rats. The parameterized model was then validated using data that measured oxidative stress and kidney injury induced by an extended course of ethylene glycol intake.

RESULTS

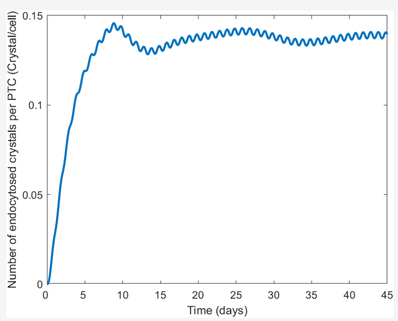
The design of the crystal nephropathy sub-model includes the formation of crystals in the tubule lumen, phagocytosis of crystals into tubule cells, oxidative stress caused by crystal uptake, crystal aggregation in the interstitial space, and the immune system reaction to crystal formation (right). PBPK modelling produced an estimate for the oxalic acid concentration in kidney tubules [1,2] (below, light blue). The sub-model was parameterized using the crystal state vs. time data after ethylene glycol administration in rats published in Vervaet 2009 [3] (below right). The model represents tubule crystal formation and adhesion well; representation of interstitial crystals is a topic for future work.

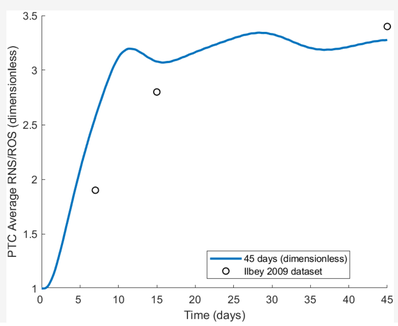


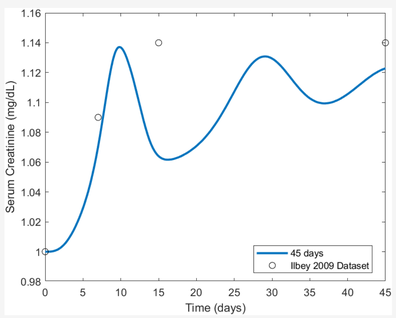




The crystal nephropathy model was validated using the extended ethylene glycol administration protocol published in Ilbey 2009 [4]. RENAsym predictions of the number of crystals (below left) replicates the oxidative stress generated by the crystals (below middle) as well as the serum creatinine elevations induced by ethylene glycol administration (below right).

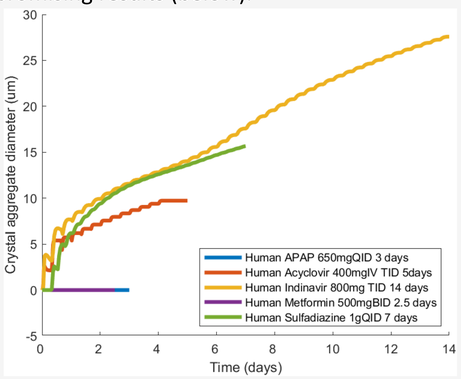






CONCLUSION

The crystal nephropathy model in RENAsym does a reasonable job of representing ethylene glycol-induced calcium oxalate crystal formation and its nephrotoxic effects. As a result, the model shows promise in its ability to predict kidney injury due to other compounds that can precipitate in the kidney tubule. The current version of RENAsym has been used to predict the potential for drug-induced crystal nephropathy in humans, with promising results (below).



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