Modeling of Indinavir-Induced Crystal Nephropathy in RENAsym®

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Abstract ID: 4478

ABSTRACT

Background: Indinavir, a protease inhibitor used to treat patients with HIV/AIDS, is known to induce crystal nephropathy. This is predominantly due to the precipitation of Indinavir in kidney tubules because of its low solubility at tubular luminal pH (pH = 5.5 to 7), approximately 30 to 35 µg/mL. Crystals can cause injury to neighboring tubular cells and can lead to tubule obstruction or crystal nephropathy. Indinavir was modeled in RENAsym®, a quantitative systems toxicology (QST) model of acute kidney injury (AKI). RENAsym contains a sub-model representing crystal formation and subsequent toxicity. Indinavir was modeled as an exemplar compound for the validation and accuracy of the crystal nephropathy sub-model.

Methods: The crystal nephropathy model within RENAsym, including crystal dynamics and tubular injury caused by crystals, was originally parameterized to an abundance of *in vivo* experiments for ethylene glycol due to a lack of preclinical data for indinavir treatment. Specific precipitation dynamics for indinavir were parameterized in human using *in vitro* precipitation experimental results[1]. A physiologically-based pharmacokinetic (PBPK) model for indinavir was constructed within GastroPlus®, and two weeks of indinavir treatment (800 mg given every 8 hours) was simulated.

Results: The predicted kidney tubule concentration-time profile was imported into RENAsym, and the RENAsym crystal nephropathy sub-model predicted a crystal aggregate size of 27 µm. A longer indinavir treatment was simulated for 6 months, and RENAsym predicted a crystal aggregate size of 71 µm. These crystal aggregate size predictions are within the literature range, which reports a crystal aggregate size range from 27 µm to 103 µm[2].

Conclusions: The crystal nephropathy model in RENAsym accurately predicted clinical outcomes related to indinavir-induced crystal nephropathy, which demonstrates the potential for RENAsym to predict the potential crystal nephropathy liability of future compounds.

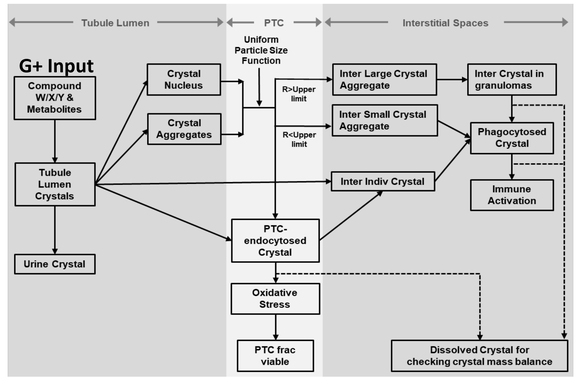
INTRODUCTION

- Indinavir is primarily used to treat HIV/AIDS and is insoluble at luminal pH (5.5 to 7) with a concentration of at least 30-35 ug/mL
- Typical regimen of Indinavir is 800 mg given every 8 hours
- Persistent exposure to crystals can damage neighboring tubular cells and lead to tubule obstruction at different points of the tubule causing crystal nephropathy
- Typical renal complications observed with Indinavir treatment include clinical presentations of crystalluria, acute kidney injury, and increased serum creatinine
- The crystal nephropathy submodel in RENAsym includes crystal formation, aggregation, clearance, and induction of oxidative stress which leads to kidney injury (Figure 1)
- Here we model Indinavir in humans as an exemplar compound to validate the crystal nephropathy submodel in RENAsym

RESULTS

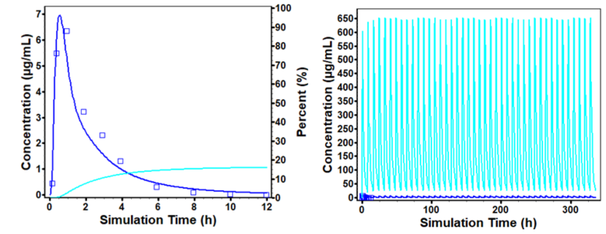
Crystal Nephropathy Submodel in RENAsym

Figure 1: The Crystal Nephropathy model in RENAsym combines toxicity studies, predictions of metabolism and distribution, as well as inner workings of kidney physiology to predict crystal dynamics and precipitation for a given drug and therefore the potential to induce renal injury.



Simulation Results of Indinavir in Baseline Individual

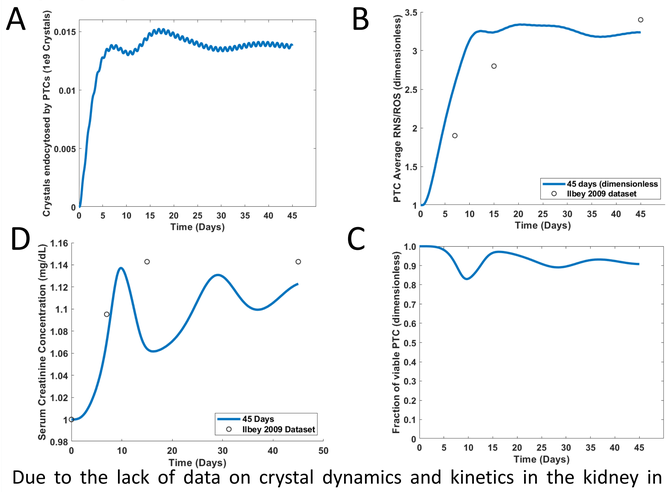
Figure 3: Simulated a single 800 mg dose of Indinavir for 12 hours resulting in a plasma concentration (dark blue in left figure) and urine output (light blue line in left figure) in line with data[3] and predicted kidney tubule concentration (right).



Using GastroPlus 9.8 we simulated a single dose of 800 mg Indinavir for 12 hours. The simulated fit aligned with literature values for plasma concentration[3]. Moreover, the urine output is also in line with data[3], being between 10-20%. The predicted kidney tubule concentration is well above solubility of Indinavir (30-35 µg/mL).

Optimization of Crystal Nephropathy Submodel based on Rats

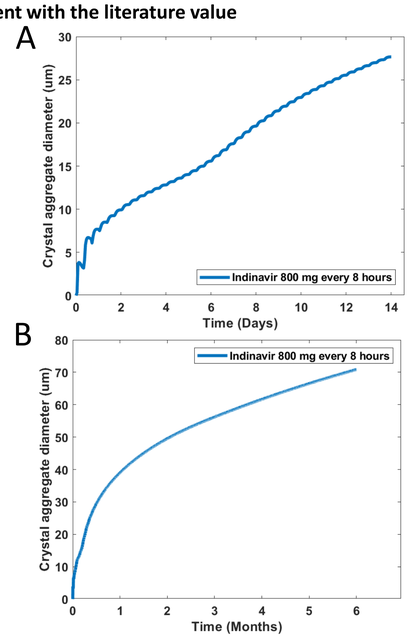
Figure 2: Parameterization and validation of crystal dynamics and kinetics leading to injury is based literature for ethylene glycol-induced crystal nephropathy in rats



Due to the lack of data on crystal dynamics and kinetics in the kidney in humans, the crystal nephropathy submodel was validated and optimized against preclinical models of crystal nephropathy. Extensive data on calcium oxalate crystal formation induced by ethylene glycol was available in rats and mice[4]. Specific crystal dynamics were modeled based on this literature[4] (Figure 2A). Since crystals can induce oxidative stress and leading to kidney injury, parameterization of this mechanism in the submodel was based on ROS levels from long-term studies in rats (45 days) to reproduce similar levels of ROS[5] (Figure 2B). This level of ROS leads to kidney injury as represented above with fraction of viable proximal tubule cells (Figure 2C), eventually leading to an increase in serum creatinine levels[5] (Figure 2D). The successful optimization was applied to humans to be able to represent clinical outcomes for Indinavir accurately.

Simulation Results of Indinavir in Baseline Individual

Figure 4: Simulations of short and long-term treatment of Indinavir in a simulated baseline individual predicts crystal aggregate sizes consistent with the literature value



Indinavir was simulated for two weeks in RENAsym in a baseline healthy individual, 800 mg every 8 hours. The predicted crystal aggregate size is 27 µm (Figure 4A). Indinavir was also simulated for a longer regimen of 6 months and the crystal aggregate size was 71 µm (Figure 4B). These clinical outcomes are in agreement with the literature value of 27 µm to 103 µm for crystal aggregate size of Indinavir crystals[2].

METHODS

- This submodel was optimized and modeled based on literature for ethylene glycol-induced crystal nephropathy in rats and mice, due to the lack of data in humans
- This optimization was applied to humans and further parameterization was validated by crystal aggregate size for Indinavir[2]
- Precipitation dynamics for indinavir were parameterized in human using *in vitro* precipitation experimental results[1] and a precipitation time was extrapolated from these results
- PBPK simulations of single and continuous dosing (two weeks and six months) of Indinavir was simulated in GastroPlus 9.8 for 800 mg every 8 hours
- Simulations predicting crystal aggregate size were performed for both treatments of Indinavir in a baseline healthy individual in RENAsym

CONCLUSION

- The crystal nephropathy submodel was successfully optimized to extensive literature on preclinical models, such as ethylene glycol-induced crystal nephropathy
- A two-week simulation resulted in a crystal aggregate size of 27 um and a six-month simulation resulted in 71 um, within the literature value range of 27 to 103 um
- The crystal nephropathy submodel successfully predicted clinical outcomes and shows potential to predict crystal nephropathy for new compounds

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ACKNOWLEDGEMENTS

- Dr. Melissa Hallow, PhD and Dr. Zheng Dong, PhD
- Supported by the National Institute Of Diabetes And Digestive And Kidney Diseases of the National Institutes of Health under Award Number R44DK118981. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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