Mechanistic Analysis of Cisplatin-Induced Acute Kidney Injury Using Quantitative Systems Toxicology Modeling

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ABSTRACT

Objectives: Acute kidney injury is a common side effect of cisplatin chemotherapy. There are several proposed mechanisms of cisplatin-induced acute kidney injury (AKI); however, there is little understanding of which of these mechanisms is the most likely contributor to the observed toxicity.

Methods: RENAsym, a quantitative systems toxicology (QST) model of drug-induced kidney injury, was constructed using elements of known kidney physiology. Mitochondrial toxicity and oxidative stress models were adapted to the kidney environment from DILIsym, a QST model of drug-induced liver injury. *In vitro* data regarding cisplatin mitochondrial toxicity and oxidative stress generation were adapted from literature sources and used as inputs into RENAsym along with a basic model of cisplatin kidney exposure.

Results: Simulations reasonably recapitulated the toxicity and dose-response observed with cisplatin in both humans and rats. In the rat, mild toxicity was predicted after a 1 mg/kg single dose and severe toxicity was predicted after a 2.5 mg/kg single dose (Figure 1), which is generally in qualitative agreement with published data (1). In the human, a decline of 17% of proximal tubule cell mass was simulated after a single dose of 533 mg/m^2 body area, which is in general agreement with the glomerular filtration rate decline reported in the literature (2). In both species, oxidative stress was shown to be the primary mechanism involved in the simulated toxicity.

Conclusions: RENAsym was used to predict the renal toxicity of cisplatin, and to suggest that cisplatin injury is primarily due to oxidative stress. QST modeling shows promise for being both a predictive and descriptive tool for drug-induced kidney injury.

OVERVIEW

- Proximal tubule cell injury plays a significant role in drug-induced AKI.
- Successful predictions of drug-induced liver injury have been made using DILIsym®, a quantitative systems toxicology (QST) model of the liver.
- Portions of the intracellular dynamics model of DILIsym, including mitochondrial bioenergetics and substrate utilization, were adapted to the case of the proximal tubule cell (see Poster W-078 for more details).
- PBPK models and exposure estimates were constructed for cisplatin in rats and humans based on literature (1).
- Cisplatin effects on toxicity mechanisms were adapted from the literature in rat and pig cells (2,3).
- Simulations conducted comparing human results to clinical data for a 533 mg/m^2 single dose and a 50 mg/m^2 one-week dosing regimen (4) and rat results to previously published calculations of cell loss after 1 and 2.5 mg/kg single doses (1).

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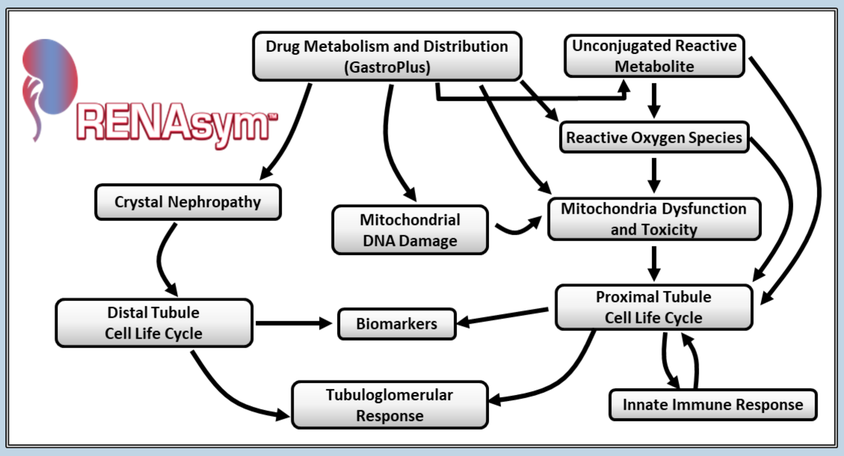
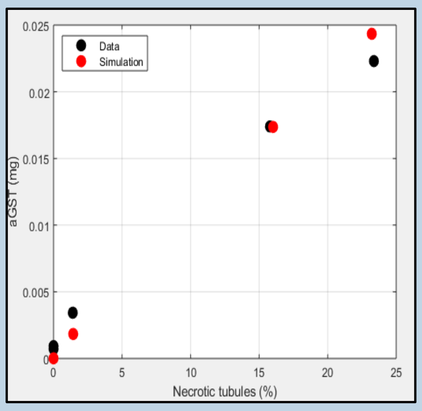
RESULTS

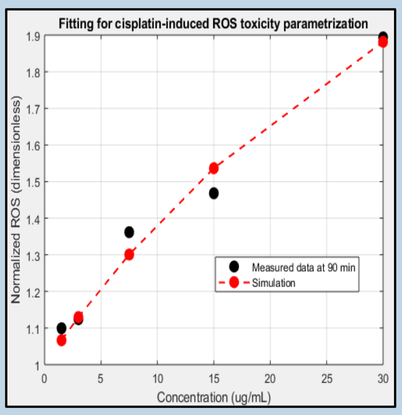
RENAsym Software





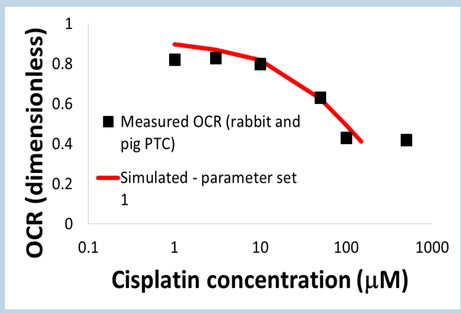
RENAsym is designed to integrate estimates of exposure, *in vitro* toxicity, and known kidney physiology (such as the relationship between cell death and αGST release, left) into an estimate of the potential for a drug to cause kidney injury.

Toxicity Parameters

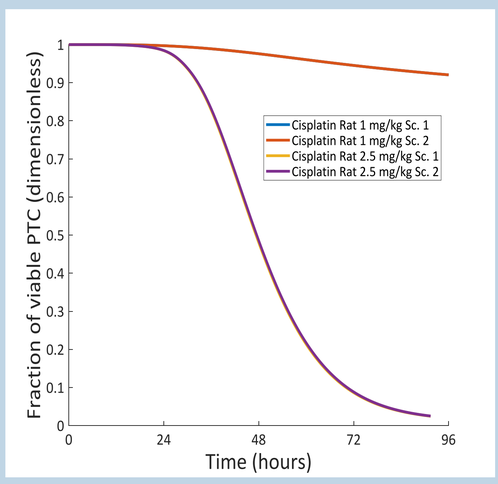


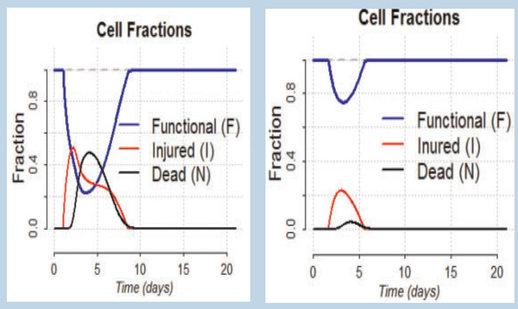
Left: Cisplatin-induced oxidative stress data in porcine proximal tubule cells (PTCs) (2) was fit in RENAsym using a simulated dosing protocol meant to mimic *in vitro* conditions. The rate constant that provided the best fit to these data was used in the rat and human simulations below.

Right: Mitochondrial toxicity data from porcine and rabbit PTCs (2,3) was fit using MITOsym, a model of *in vitro* mitochondrial bioenergetics (5); rate constants for ETC inhibition from MITOsym were converted to RENAsym parameters using a conversion factor.



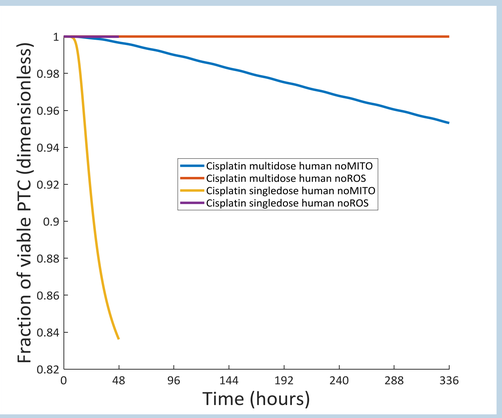
Simulation Predictions





Left: Simulations in the rat predicted a loss of about 8% of PTCs after a 1 mg/kg dose and a near-complete loss of PTCs after a 2.5 mg/kg dose. This aligns favorably with results from the literature, where a 1 mg/kg dose led to mild injury while a 2.5 mg/kg dose led to severe injury (1).

Right: Simulations in the human predicted a loss of 17% of PTCs after a 533 mg/m^2 single dose. A compilation of single-dose clinical data showed a loss of glomerular filtration rate of 8-30% with a median of 21.5% after a single dose of cisplatin; the average single dose given in these studies was 533 mg/m^2. Significant loss was also reported after repeated 50 mg/m^2 daily dosing (4), which suggests the simulation may be underpredicting in the multiple-dose case. The underlying mechanism of the toxicity was predicted to be oxidative stress; markers of mitochondrial function remained intact during the simulation.



Dosing protocol	Predicted cell loss	Clinical loss of function (4)
533 mg/m^2 single dose	17%	8-30%, median 21.5%
50 mg/m^2 QD, 1 week	5%	N/A, significant loss reported

Compound	Mitochondrial dysfunction signals	Oxidative stress signals
Cisplatin	None (at the studied dose)	Yes

CONCLUSIONS

- Cisplatin-induced injury was reasonably recapitulated by the simulations in both rat and human.
- Cisplatin-induced injury was predicted to be mostly the result of oxidative stress.
- These results prove that the RENAsym concept could be used to predict drug-induced AKI.
- Future work is underway, including a more complex model of kidney physiology, collection of higher-quality cisplatin *in vitro* data, and the exploration of other compounds and other mechanisms of renal toxicity.

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REFERENCES

1. Gebremichael Y, et al. Toxicol Sci. 2018 01;162(1):200–11.
2. Kruidering M, et al. J Pharmacol Exp Ther. 1997 Feb;280(2):638–49.
3. Beeson CC, et al. Anal Biochem. 2010 Sep 1;404(1):75–81.
4. Hartmann JT, et al. Int J Cancer. 1999 Dec 10;83(6):866–9.
5. Yang Y, et al. Pharm Res. 2015 Jun;32(6):1975–92.

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