Evaluating Nephrotoxicity of Cisplatin in Rats with RENAsym, a Mechanistic Model of Drug-Induced Acute Kidney Injury

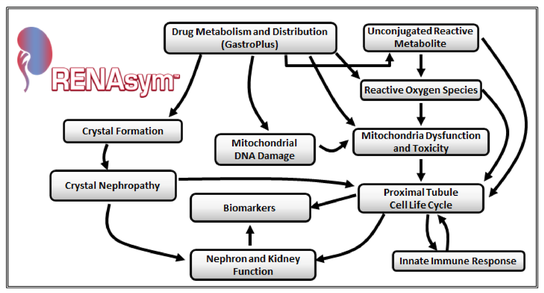
Nader Hamzavi[a], Jeffrey L. Woodhead[a], and Brett A. Howell[a]
[a]DILIsym Services Division, Simulations Plus, Research Triangle Park, NC

Abstract: 4710

INTRODUCTION

- Acute kidney injury (AKI) is often initiated by cellular toxicity of proximal tubule epithelial cells (PTEC) when exposed to nephrotoxic drugs such as cisplatin.
- Cisplatin-mediated toxicity ranges from mild PTEC injury to cellular death via several cellular damage mechanisms in association with doses of cisplatin.
- The pathophysiology of cisplatin-induced AKI (cellular, neurohormonal, and hemodynamic) resulting in impaired filtration is a complex process which has not been completely understood.
- RENAsym has been developed as a quantitative systems toxicology model for the prediction of drug-induced AKI by translating cellular-level *in vitro* mechanistic data to systems level manifestations of AKI.
- Our aim is to predict cellular and hemodynamic responses of cisplatin-induced AKI across species and at multiple doses using RENAsym.

METHODS

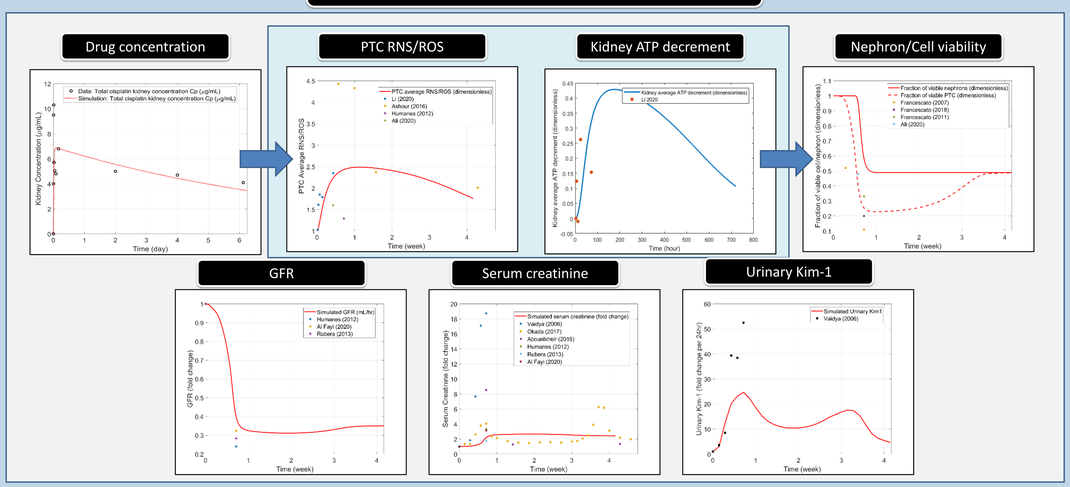


- RENAsym has been developed to connect key cellular injury mechanisms with renal hemodynamic responses.
- RENAsym is a multiscale model which represents the RPTEC life cycle, bioenergetics, and immune responses to drug-induced toxicity. These cellular injury mechanism liabilities were quantified for cisplatin using *in vitro* assays.
- RENAsym also represents renal function at the systems level, and feedback mechanisms for renal hemodynamics including tubuloglomerular feedback (TGF) and renin-angiotensin-aldosterone systems (RAAS).
- The renal hemodynamic responses of drug induced RPTEC injury were represented in RENAsym and characterized for humans and rats treated with nephrotoxic drugs including cisplatin.

RESULTS

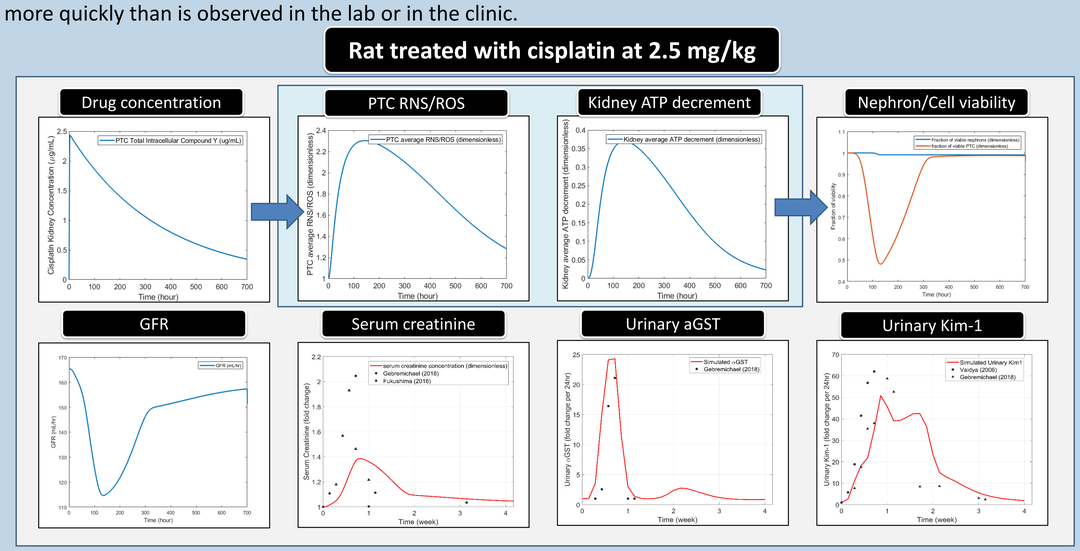
- A PBPK model was built and optimized to the observed plasma and kidney concentration of cisplatin.
- *In vitro* measurements of oxidative stress and mitochondrial dysfunction were collected by Cyprotex and translated into inputs for RENAsym.
- The model representation was optimized to cellular measurements (ROS and ATP) in rats treated with cisplatin at 5mg/kg.
- At 5 mg/kg, simulation results of GFR, and fraction of viable nephrons and PTEC in cisplatin mediated rats match well with the observed data on filtration rate and histopathology scores of tubules with necrotic cells, respectively.
- The level of predicted urinary Kim-1 at 5mg/kg reflects a delay implemented in the regeneration model of PTECs during AKI which is not well supported by Kim-1 data but agrees with the level of GFR loss and serum Cre increase.

Rat treated with cisplatin at 5 mg/kg



- Compared to 5 mg/kg cisplatin where PTC loss is substantial, 2.5 mg/kg cisplatin in rats predicts a mild injury with almost full recovery of PTCs and GFR after a significant loss predicted on day 5 post treatment.
- The biomarker submodel was optimized to urinary biomarker data (such as KIM-1 and αGST) at 2.5 mg/kg.
- RENAsym simulations suggest that cisplatin toxicity can be explained by ROS increase alone, while mitochondrial toxicity produces a signal that manifests more quickly than is observed in the lab or in the clinic.

Rat treated with cisplatin at 2.5 mg/kg



CONCLUSION

- Cisplatin-mediated toxicity in rats at cellular and system levels in healthy and pathologic states were studied using a quantitative systems toxicology model of drug-induced acute kidney injury (RENAsym).
- Cellular injury as well as renal hemodynamic responses were represented in RENAsym and validated with preclinical cellular measurements and organ-wide toxicity data in rats treated with multiple doses of cisplatin.
- Oxidative stress generated by cisplatin can explain the observed AKI; the mitochondrial dysfunction signals observed *in vitro* require further mechanistic investigation to better understand their role in cisplatin-mediated kidney injury.
- AKI injury level and regeneration of PTEC will be reexamined for future versions of RENAsym to improve our prediction of functional and urinary biomarkers across multiple doses of cisplatin.
- Simulated populations rather than the baseline individual can help us explain the inter-individual variability and variability in biomarker data.
- This work demonstrates that RENAsym is a promising tool to predict the incidence of nephrotoxicity and contribute to better understanding of the mechanisms of drug-induced AKI.

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