Evaluating the Nephrotoxicity of Exemplar Compounds Using a Mechanistic Model of Drug-Induced Acute Kidney Injury

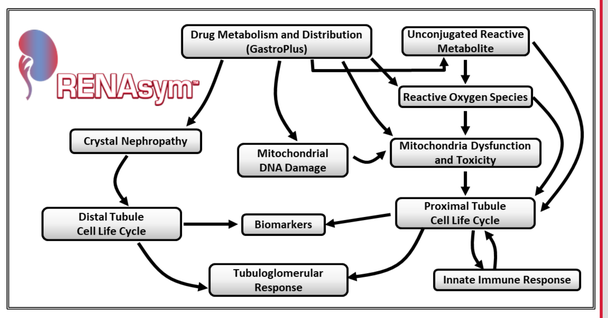
Yeshitila Gebremichael, Jeffery L. Woodhead, Nader Hamzavi, Shailendra Tallapaka, Scott Q. Siler, and Brett A. Howell

DILIsym Services, Inc., a Simulations Plus company, Research Triangle Park, NC, USA

BACKGROUND

- Drug-induced nephrotoxicity is a common source of acute kidney injury (AKI) and a condition that complicates clinical outcomes of vulnerable patients.
- Drugs cause nephrotoxicity by various cellular mechanisms, including mitochondrial dysfunction, oxidative stress, and others.
- Predicting the toxicity and injury mechanisms of drugs remains a challenge.
- We utilized a quantitative systems toxicology (QST) model to evaluate the nephrotoxicity and underlying mechanisms of two positive (cisplatin and gentamicin) and one negative (acetaminophen) control exemplar compounds.

METHODS



- We employed RENAsym™, a QST model of drug-induced acute kidney injury that is currently under development.
- RENAsym™ represents aspects of renal proximal tubule epithelial cells (PTCs), including cell life cycle, bioenergetics, drug-induced cell death pathways, and biomarker (αGST) responses.
- In vitro data from the literature was utilized to parameterize the oxidative stress (RNS/ROS) production and clearance of compounds as well as the effect of drugs on mitochondrial dysfunction (e.g., electron transport chain (ETC) inhibition).

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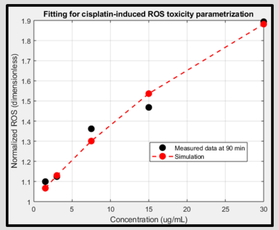
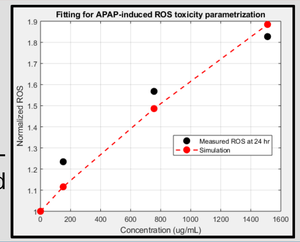
RESULTS

Oxidative Stress Parametrization

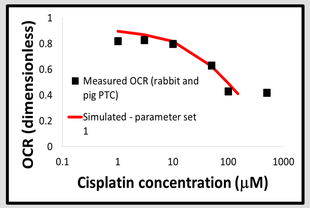


Left: Cisplatin-induced oxidative stress data in porcine PTCs (1) was fit in RENAsym™ to parameterize cisplatin-induced RNS/ROS production.

***Right*:** Acetaminophen-induced oxidative stress data in cultured HK-2 cell line (2) was fit in RENAsym™ to parameterize APAP-induced RNS/ROS production.



ETC Inhibition Parametrization



Cisplatin-induced ***(left)*** mitochondrial toxicity data from porcine and rabbit PTCs (1,3) and acetaminophen-induced ***(right)*** mitochondrial toxicity data from HepG2 (measured by Cyprotex, Inc.) was fit using MITOsym, a model of *in vitro* mitochondrial bioenergetics (4).

- *Rate constants for ETC inhibition from MITOsym were converted to* RENAsym™ *parameters using a conversion factor.*

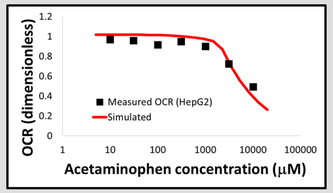
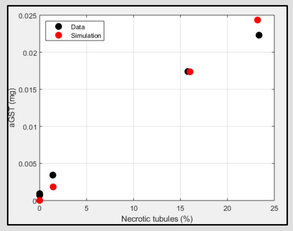


Table: Summary of toxicity parameters for drug-induced mitochondrial dysfunction and oxidative stress production. The parameters are determined by fitting in vitro data from the literature using RENAsym™. These parameters are incorporated in RENAsym™ for predicting drug-induced AKI.

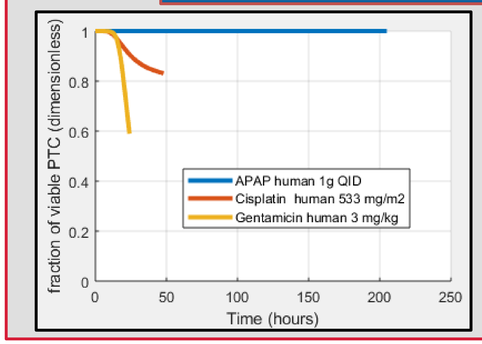
Mechanism	Parameter	Unit	Value		
			Cisplatin	APAP	Gentamicin
Mitochondrial Dysfunction	Coefficient for ETC inhibition 1	μM	12	125.9	1522
	Coefficient for ETC inhibition 3	μM	0.0518	N/A	N/A
	Max inhibitory effect for ETC 3	dimensionless	0.321	N/A	N/A
Oxidative Stress	RNS/ROS production rate Vmax 4	1/hour	12.3	0.503	0.667
	RNS/ROS production rate Km 4	mM	178.5	80879	89.4
	RNS/ROS production rate Hill 4	dimensionless	1	0.9	1

Biomarker Response Parameterization

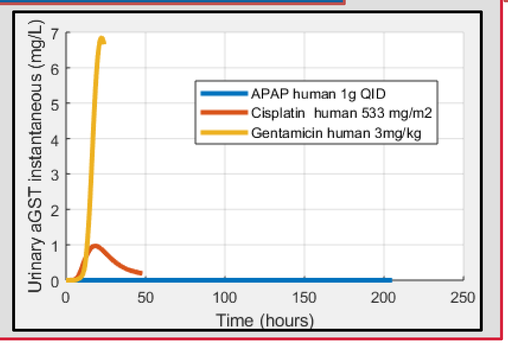
- RENAsym™ is designed to integrate drug exposure, *in vitro* toxicity, and kidney physiology to predict drug-induced AKI.
- Urinary biomarkers offer early detection of AKI. αGST is a key biomarker that signals cellular death.
- The relation between cell death and αGST (***right***) is parameterized using literature data (5)



Simulation Predictions for Exemplar Compounds



- Toxic response of simulated baseline human exposed to positive and negative control exemplar compounds .
- Fractional loss of viable proximal tubule cells (***left***) and elevations of αGST (***right***) in human model with multiple dose of 1 g QID APAP, and single doses of 533 mg/m2 cisplatin and 3 mg/kg gentamicin.



CONCLUSION

- Simulation results show no cell death or αGST elevations from exposure to a negative control compound APAP.
- Mild to significant cell death and αGST elevations were observed from exposure to cisplatin and gentamicin, the two positive control compounds.
- The model reproduces the expected qualitative features of the positive and negative control compounds.
- Oxidative stress is found to be the dominant mechanism for both cisplatin and gentamicin.
- For a more accurate quantitative predictions, effort is underway in utilizing PTC *in vitro* toxicity data for model parametrization.

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