Repeated Dose Pharmacokinetics in Rats for Identification of Novel Drug-Induced Nephrotoxicity Biomarkers

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Objectives: Nephrotoxicity is monitored using serum creatinine (SCr) and blood urea nitrogen (BUN). However, kidney damage is not detected until significant changes in levels of SCr and BUN are observed due to the time lag between kidney damage and increase in biomarker levels. This led to identification of novel biomarkers using proteomics and metabolomics, which show early signs of kidney damage in rodents. However, translating the findings to humans is lacking. The objective of this project was to identify biomarkers to detect early drug-induced nephrotoxicity in rodents using cisplatin as an exemplar and to translate those changes to humans using quantitative modeling approaches.

Methods: An LC-MS/MS method was developed and validated using Agilent-QQQ-6460 for quantitative determination of cisplatin. Pharmacokinetic (PK) studies were performed in Sprague–Dawley rats (n=4-7) and doses of 0.5, 3.5, and 7.0 mg/kg of cisplatin/blank-saline were administered via jugular vein. On days 1, 7, 14 and 21, blood and urine was collected. Rats were sacrificed on different days to extract kidney tissues. Samples were aliquoted into two, one for analysis of cisplatin, other for metabolomics using Agilent-QTOF-6540.

Results: Developed cisplatin method was validated to meet FDA guidelines for bioanalytical method validation, LOD was 1 ng/ml, calibration range 5-3000 ng/ml, and parameters such as accuracy, precision were within ±15% deviation. The method was applied to analyze plasma, urine and kidney samples from rats. PK parameters were determined by non-compartmental analysis using Phoenix64, resulted in AUC of 0.35±0.02 µg/mL*h and CL of 1676±231 ml/h/kg.

Conclusions: PK parameters obtained in-house were similar to reported literature values of different dosing groups. Furthermore, a PBPK model will be developed using cisplatin concentrations obtained in plasma, urine and kidney in rats linked to metabolomic changes. This model will be applied and evaluated in humans using literature data to predict early drug induced nephrotoxicity.