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Renal elimination of aristolochic acid I in the isolated perfused kidney model

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Aristolochic acids (AAs) are powerful nephrotoxin and human carcinogen associated with chronic kidney disease and upper urinary tract urothelial carcinomas. Aristolochic acid I (AA-I) is the most abundant type of the aristolochic acids. Published data suggest that AA-I is a substrate for renal organic anion transporters (OATs). However, the mechanisms contributing to the renal excretion of AA-I are not totally understood. In this investigation, the renal handling of AAI was evaluated in isolated perfused rat kidney (IPK) model. IPK experiments were performed to characterize the renal excretion of AAI and to probe mechanism of AAI excretion. In phase I studies AA- I was added as a bolus dose, targeting an initial concentration of 20 μM. In phase II AA-I was co-perfused with probenecid, a classic OAT inhibitor. AA-I demonstrated net reabsorption by the kidney. Co-administration of probenecid increased the renal clearance and excretion ratio of AA-I ~2-fold. Mean total recovery (% dose) of AA-I from perfusate and urine increased from 80.2% to 93.5% in IPK experiments with probenecid. Overall, this study generated important information on renal handling of AA-I. OATs on the luminal membrane of the kidney may provide an apical backflux pathway for AA-I in renal proximal tubules (urine to kidney). While these preliminary IPK findings suggest that transport inhibition is a potential strategy to attenuate AA-I nephrotoxicity, additional studies are needed to identify the specific transport systems involved in AA-I renal disposition and to explore whether transport inhibition can reduce drug uptake into the kidney.

Biography

Mariana Babayeva MD, PhD is an Associate Professor at Touro College of Pharmacy, New York City. In addition to her role at Touro, she is also a visiting Scientist at Arnold and Marie Schwartz School of Pharmacy of LIU, an Adjunct Professor at Rockefeller University, and Instructor at UNC, Eshelman School of Pharmacy. She has over 10 years of clinical experience. She is recognized for her expertise in the pharmacokinetics of renal excretion and the use of animal and organ models to explore mechanism and kinetics of renal clearance. She has conducted several international research projects. She has published in peer-reviewed journals focusing on pharmacokinetics of various drugs.

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