Altered Cisplatin Pharmacokinetics during Nonalcoholic Steatohepatitis Contributes to Reduced Nephrotoxicity

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Cisplatin is an alkylating antineoplastic agent that is indicated for the treatment of solid malignancies. Cisplatin is preferentially eliminated from systemic circulation via tubular secretion, whereby it exhibits dose-limiting nephrotoxicity. Interindividual variability in xenobiotic transporter expression is a known contributor to differential cisplatin toxicity and efficacy, and may be the result of genetic, environmental, and pathological contributions. In this study, we aimed to determine if nonalcoholic steatohepatitis (NASH) alters cisplatin pharmacokinetics and if this change elicits differential nephrotoxicity. Sprague Dawley rats fed a control or methionine and choline deficient (MCD) diet to model NASH were given a single bolus dose of cisplatin and sacrificed after 72 h. The MCD diet resulted in a NASH hepatic phenotype that remained unchanged following cisplatin exposure. Drug-naïve NASH rats also displayed no evidence of differential renal pathology relative to control rats. However, renal necrosis and inflammation were reduced in NASH by 40 and 63% following cisplatin treatment, respectively, relative to healthy controls. Furthermore, kidney weights of cisplatin-treated control rats were increased by 31%, compared to an 18% increase in NASH. Plasma cisplatin clearance was reduced from 6.78 (control) to 4.04 mL/min in NASH, and cisplatin plasma AUC was significantly increased by 44% in NASH, relative to control. Cumulative urinary elimination of cisplatin was decreased from 73 to 34% of total dose and renal clearance was reduced from 4.64 to 1.49 mL/min in NASH, compared to control. Subsequently, renal intracellular accumulation of cisplatin after 6 h was reduced by 34% in NASH, relative to control. Supporting these findings, expression of proximal tubule cisplatin uptake transporters, Ctr1 and Ctr2, were reduced by 24 and 64%, respectively compared to healthy control rats, whereas expression of Oct1, Oct2, and Oct3 were unchanged. Interestingly, expression of cisplatin efflux transporters Mate1 and Atp7a were reduced by 52 and 31%, respectively, in NASH compared to control. Taken together, these data suggest that NASH alters renal uptake and efflux transporter expression, thereby attenuating cisplatin uptake and clearance in the kidney with a corresponding reduction in renal cell exposure and nephrotoxicity during NASH. As such, this study demonstrates that NASH can influence pharmacokinetics of renally-eliminated drugs which may contribute to adverse drug reactions.