IN Volvement of organic anion transporters in the renal secretion of topotecan
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Topotecan, a topoisomerase I inhibitor, is a semisynthetic water-soluble and cationic analog of camptothecin. Topotecan has a lactone moiety and exhibits a reversible pH-dependent hydrolysis between the lactone and hydroxyl acid forms. Data from a pediatric study showed renal clearance exceeds GFR and suggested that tubular secretion and/or hepatobiliary excretion in addition to GFR were involved in topotecan clearance. A mouse study reported that probenecid increases plasma concentrations presumably by inhibiting the tubular secretion of topotecan (HAT > lactone). However, the exact mechanism of renal elimination of topotecan has not been identified molecularly. Accordingly, in the present study, the transport of HAT across the renal basolateral membrane was investigated using rat kidney slices and transporter-expressing Xenopus oocytes. HAT was taken up by kidney slices in a time- and concentration-dependent manners. The uptake was reduced by both PAH and pravastatin, a relatively selective substrate of rat organic anion transporter 1 (rOAT1) and rOAT3, respectively, but not by excess TEA, a substrate of organic cation transporters (rOCT1 and rOCT2). Human OAT3 but not human OCT2 transported HAT by Xenopus oocytes. These results suggested that the urinary excretion of HAT is accounted for by organic anion transporter(s) as well as GFR. These findings will be useful for considering potential dose modifications when topotecan is given with certain concomitant medications.

Role of organic anion transporters on pharmacokinetics of zonampanel, an α-amino-3-hydroxy-5-methylisoxazole-4-propionate receptor antagonist, in rats
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Zonampanel monohydrate (YM872) is a novel α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor antagonist. In humans, the major elimination route for zonampanel has been reported to be the urine via the kidneys. In addition, it has also been reported that zonampanel, which is negatively charged at physiological pH, is transported by human organic anion transporter 1 (OAT1), OAT3 and OAT4 (but not transported by OAT2), suggesting contribution of these OATs to the renal excretion. In rats, zonampanel is also dominantly eliminated via urine but partly via bile as the unchanged form. Its high renal clearance suggests the contribution of renal tubular secretion. Moreover, OAT inhibitors probenecid and cimetidine decreased the renal clearance of zonampanel in rats. The purpose of this study is to elucidate the molecular mechanism of the excretion of zonampanel using cells stably expressing rat Oat1, Oat2, and Oat3. Zonampanel inhibited the uptake of prototypical organic anion substrates, [3H]para-aminomhippurate in rat Oat1 and [14C]salicylic acid in rat Oat2, and [3H]estrone-3-sulfate in rat Oat3. A time- and saturable concentration-dependent increase in [14C]zonampanel uptake was observed in these cells. Considering the tissue distribution and localization of each transporter, these results suggest that zonampanel is taken up via rat Oat1 and Oat3 from the blood into proximal tubular cells and via rat Oat2 and Oat3 from the blood into the hepatocytes. Probenecid and cimetidine inhibited [14C]zonampanel uptake by the rat Oats, which explained the observations in in vivo described above.