SEARCH AND VALIDATION OF IN VIVO PROBE DRUGS FOR FUNCTIONAL ANALYSIS OF OAT1 AND OAT3 IN HUMANS

Ying Tian, Kazuya Maeda, Yuji Kumagai, Tsunenori Kondo, Hitoyuki Kusuhara and Yuichi Sugiyama

1Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, 113-0033, Japan
2Kitasato University East Hospital, 2-1-1, Asamizodai, Sagamihara, Kanagawa, 228-8520, Japan
3Department of Urology, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, 162-8666, Japan

Organic anion transporter (OAT)1 and OAT3 are responsible for the renal uptake of organic anions including several clinically prescribed drugs. The purpose of this study was to validate suitable probe drugs or specific inhibitors for OAT1 and OAT3 that can be used to evaluate the function of each transporter in clinical situations. We selected adefovir and benzylpenicillin (PCG) as specific substrates for OAT1 and OAT3, respectively. To confirm their substrate specificities, we observed their uptake in OAT1- and OAT3-expressing human embryonic kidney-293 cells and also evaluated the inhibitory effects of p-aminohppurate (PAH, a specific inhibitor for OAT1) and probenecid (a global inhibitor of anion transport) on the uptake of adefovir and PCG in human kidney slices. Furthermore, we performed a human clinical study to observe the effects of coadministration of PAH and probenecid on the pharmacokinetics of adefovir and PCG. In vitro results revealed that adefovir and PCG are specific substrates for OAT1 and OAT3, respectively. Probenecid potently inhibited adefovir and PCG uptake, with Ki values of less than 5 μM in human kidney slices. In contrast, PAH preferentially inhibited OAT1-mediated adefovir uptake rather than OAT3-mediated PCG uptake, suggesting that PAH may be used as a specific inhibitor of OAT1 in clinical situations. The results of the clinical study suggested that the renal clearance of adefovir was inhibited by probenecid and PAH. The renal clearance of PCG was decreased by probenecid; however, it was unexpectedly increased by PAH, possibly because PAH inhibits the reabsorption process of PCG. Therefore, PCG may not be a suitable probe drug for OAT3.

WHY DO MUTATIONS IN OATP1B3 AND MRP2 AFFECT DOCETAXEL-INDUCED NEUTROPENIA?

Akihiro Yamada, Kazuya Maeda, Taisei Mushiroda, Yusuke Nakamura and Yuichi Sugiyama

1Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo, 113-0033, Japan
2Laboratory for Pharmacogenetics, Center for Genomic Medicine, The Institute of Physical and Chemical Research (RIKEN), Yokohama 230-0045 and 3Laboratory of Molecular Medicine, Human Genome Center, Institute of Medical Science, The University of Tokyo, Tokyo 108-8639, Japan

Neutropenia is one of the most important dose-limiting toxicities in patients treated with anticancer drugs. Recently, Kiyotani et al. demonstrated that the incidence of severe hematopoietic toxicity in patients taking docetaxel was significantly associated with genetic polymorphisms of organic anion transporter peptide (OATP) OATP1B3 and multidrug-resistance-associated protein-2 (MRP2) (Kiyotani K et al., Cancer Sci. 99(5):967–72 (2008)). Although docetaxel is a substrate of these transporters, the roles of these transporters in the side effects of docetaxel are not clear. Therefore, the purpose of this study was to investigate the impact of OATP1B3 and MRP2 on the pharmacokinetics and hematopoietic toxicity of docetaxel. Expression of OATP1B3, but not OATP1B1, in human embryonic kidney-293 cells significantly enhanced the uptake of docetaxel, suggesting that docetaxel is taken up into human hepatocytes mainly via OATP1B3. Docetaxel was administered to Sprague-Dawley (SD) rats and Eisai hyperbilirubinemic rats (EHBRs) by in vivo infusion (30 μg/min/kg). Total plasma clearance of docetaxel in EHBRs (35 ± 0.7 mL/min/kg) was significantly lower than in SD rats (56.1 ± 4.1 mL/min/kg). In contrast, only 6.44 % of administered docetaxel was excreted into bile in an unchanged form. Bone marrow-to-plasma and liver-to-plasma concentration ratios were not significantly different. It has been reported that docetaxel is not excreted into urine in humans and rats. Taking these results into consideration, it is likely that the lack of MRP2 does not affect the pharmacokinetics of docetaxel. One possible explanation for our results is that hepatic uptake of docetaxel is inhibited by endogenous compounds, such as bilirubin, and/or metabolic activity is lower in EHBRs. Further experiments are needed to explain the decreased clearance of docetaxel in EHBRs.