INVESTIGATION OF THE INHIBITORY EFFECTS OF VARIOUS THERAPEUTIC DRUGS ON OATP1B3-MEDIATED UPTAKE OF FEXOFENADINE
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Fexofenadine (FEX), a non-sedating antihistamine drug, is an effective treatment for seasonal allergic rhinitis and chronic urticaria. FEX is known to undergo hardly any metabolism and is excreted mainly into the bile in unchanged form. It has been reported that coadministration of various drugs (erythromycin, azithromycin, ketoconazole, itraconazole, verapamil, ritonavir and lopinavir) results in an increase in the plasma AUC of FEX. One possible mechanism for this is thought to be the inhibition of intestinal P-gp activity, which can enhance the absorption of FEX. However, the inhibition of its hepatic uptake should be also taken into account. We previously showed that organic anion transporting polypeptide 1B3 (OATP1B3) mainly contributes to the hepatic uptake of FEX in humans. In the present study, the inhibitory effects of various therapeutic drugs on the FEX uptake in OATP1B3-expressing cells were investigated and the clinical significance of in vitro inhibitory effects was also discussed by considering the maximum unbound concentration at the inlet to the liver (Iu,in,max). Comparing the inhibition constants (Ki values) for OATP1B3 with Iu,in,max, some drugs (cyclosporin A, rifampicin, azithromycin) have the potential to interact with OATP1B3-mediated uptake of fexofenadine. However, other drugs, some of which have been reported to cause a drug interaction with FEX in clinical situations, may not inhibit OATP1B3 at their clinical concentrations. These results suggest that in some cases, the inhibition of the hepatic uptake of FEX is partly involved in the drug interaction, but for the most part, other mechanisms such as inhibition of the intestinal P-gp should be also considered.

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CEFTRIAXONE IS A POTENT SUBSTRATE OF HUMAN MRP4 AND ITS TRANSPORT IS INHIBITED BY VANCOMYCIN, FUROSEMIDE, BUMETANIDE AND ETHACRYNIC ACID
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Drug-drug interaction of ceftriaxone with vancomycin, fosfomycin and furosemide has been reported, restricting the possible combination therapy of these drugs. Previously, we have reported that cefmetazole is a strong substrate of human multi-drug resistance associated protein 4 (hMRP4/ABCC4). Therefore, there would be strong possibilities that ceftriaxone is also a substrate of hMRP4 and the reported drug-drug interaction may be ascribed to the inhibition of hMRP4 mediated transport. The purpose of this study was to clarify whether ceftriaxone is a substrate of human hMRP4 and vancomycin, fosfomycin, furosemide, bumetanide and ethacrylic acid would inhibit the transport of ceftriaxone mediated by hMRP4. Ceftriaxone was significantly taken up into hMRP4 expressing Sf9 vesicles compared with mock vesicles in osmolarity-dependent manner. The uptake of ceftriaxone by hMRP4 was concentration dependent with K_m value of 19 μM, which is more than ten-fold lower than that of MTX (K_m=220 μM), indicating that ceftriaxone is a potent substrate of hMRP4. Known MRP4 inhibitors, probenecid (500 μM), dicyproamide (1 μM), indomethacin (50 μM) and diclofenac (100 μM), significantly inhibited the uptake of ceftriaxone by hMRP4 expressing vesicles by up to 93%. Vancomycin (50 μM), furosemide (5 μM), bumetanide (0.5 μM), ethacrynic acid (5 μM) significantly inhibited the ceftriaxone uptake, while fosfomycin (2 mM) did not show significant inhibition. In conclusion, ceftriaxone is a substrate of hMRP4 and vancomycin, furosemide, bumetanide and ethacrylic acid inhibit the hMRP4 mediated transport of ceftriaxone.