The Involvement of Transporters in Clinically Relevant Drug-Drug Interactions

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Cerivastatin, an HMG-CoA reductase inhibitor, was withdrawn from the market, due to a clinically reported severe side effect of myotoxicity. This side effect was sometimes associated with a pharmacokinetic alteration caused by a drug-drug interaction (DDI). At that time, the likelihood of drug-drug interactions with cerivastatin was believed to be low because of its dual metabolic pathway mediated by cytochrome P450 2C8 and 3A4. Thus, we studied the mechanism of clinically relevant DDI of cerivastatin with cyclosporin A (CsA), focusing on the possibility of inhibition of transporters. We examined the effect of CsA on the uptake of cerivastatin into cryopreserved human hepatocytes and found that CsA inhibited it in a concentration dependent manner. The obtained IC_{50} value was lower than the plasma unbound concentration of CsA in clinical situations, suggesting a possibility of clinically relevant DDI associated with the transporter-mediated hepatic uptake. On the other hand, CsA did not inhibit the metabolism of cerivastatin at the therapeutic concentrations. Thus, we found that DDI between cerivastatin and CsA was mainly due to the inhibition of transporter-mediated hepatic uptake. Currently, CsA is well known inhibitor of organic anion transporting polypeptide 1B1 (OATP1B1). In addition, there are some reports of therapeutic drugs which inhibit OATP1B1 at their therapeutic concentrations. We can predict the possibility of DDI by the IC_{50} values obtained in *in vitro* studies and therapeutic unbound concentrations. Thus, we believe such information will help to prevent from severe DDIs.