PHYSIOLOGICALLY BASED PHARMACOKINETIC MODELING INCLUDING TRANSPORTER-MEDIATED MEMBRANE TRANSPORT PROCESSES
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Physiologically based pharmacokinetic (PBPK) modeling allows us to predict drug concentration profiles in plasma and target organs, and provides a better understanding of the parameters that are important for pharmacokinetics. A number of studies have demonstrated that drug transporters play important roles in the pharmacokinetics of drugs, however, a PBPK model based on information on transporters has not been developed. The purpose of this study is to establish a PBPK model that includes transporter-mediated saturable membrane transport processes, and to investigate the effect of changes in transporter function on the pharmacokinetics and, ultimately, the pharmacological and/or toxicological effects of drugs. Pravastatin, an HMG-CoA reductase inhibitor, the distribution and excretion of which are governed mainly by transporters, was selected as a test compound. The plasma and tissue concentration profiles were simulated at various doses using parameters obtained experimentally in rats or cited from previous studies. The simulated data were comparable with the observed data that exhibited non-linear pharmacokinetics. Enterohepatic circulation had a minimal effect on the plasma concentration in both simulations and actual measurements. Sensitivity analyses were performed. The hepatic uptake process governs the plasma concentration, but is not related to the liver concentration as far as the extrahepatic clearance is negligible. On the other hand, the canalicular efflux governs the liver concentration, but hardly affects the plasma concentration. Accordingly, this PBPK model can be applied to predict changes in drug concentrations in plasma and target organs caused by changes in transporter function and expression levels.

A RAPID AND COMPREHENSIVE SUBSTRATE/NON-SUBSTRATE CLASSIFICATION FOR HUMAN MRP4 TRANSPORTER BY MEANS OF LC-MS/MS-COCKTAIL METHOD
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Development of a rapid substrate/non-substrate classification method has been a crucial issue for drug transporter scientists. The purpose of this study was to develop a rapid and comprehensive substrate/non-substrate classification method (LC-MS/MS-Cocktail Method) for human multidrug resistance associated protein 4 (MRP4). Human MRP4 expressing Sf9 vesicles were incubated with mixture of methotrexate (MTX) as an internal reference, and 49 compounds which have not been reported as MRP4 substrate. Membrane Uptake Index Difference (MUID) was determined by subtracting uptake amount into mock vesicles from that into MRP4 expressing vesicles determined by multichannel LC-MS/MS. In 1st screening, 7 substrate candidates, including cefmetazole and rebamipide as promising candidates, have been found. 5 substrate candidates were found at 2nd screening. At 3rd screening, the remaining 33 compounds were divided into 4 groups. No significant transport was observed for 16 compounds in 2 groups. Transport of MTX was not significantly inhibited in these 2 groups, supporting that these 16 compounds are not MRP4 substrates. 4th screening was performed for the remaining 2 groups. Significant transport was demonstrated for 8 compounds, while the remaining 9 compounds failed. No significant osmotic pressure effect demonstrated that meloxicam and nateglinide were not MRP4 substrates. In conclusion, at least 14 substrates and 27 non-substrates for MRP4 were identified. 4 compounds were under detection limit. LC-MS/MS-Cocktail Method combined with osmotic pressure studies is an efficient strategy to rapidly classify compounds into substrate and/or non-substrate for ABC transporters.