Quantitative Analyses of Hepatic OATP-Mediated Interactions Between Statins and Inhibitors Using PBPK Modeling With a Parameter Optimization Method

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This study aimed to construct a widely applicable method for quantitative analyses of drug–drug interactions (DDIs) caused by the inhibition of hepatic organic anion transporting polypeptides (OATPs) using physiologically based pharmacokinetic (PBPK) modeling. Models were constructed for pitavastatin, fluvastatin, and pravastatin as substrates and cyclosporin A (CsA) and rifampicin (RIF) as inhibitors, where enterohepatic circulations (EHC) of statins were incorporated. By fitting to clinical data, parameters that described absorption, hepatic elimination, and EHC processes were optimized, and the extent of these DDIs was explained satisfactorily. Similar *in vivo* inhibition constant (K_i) values of each inhibitor against OATPs were obtained, regardless of the substrates. Estimated K_i values of CsA were comparable to reported *in vitro* values with the preincubation of CsA, while those of RIF were smaller than reported *in vitro* values (coincubation). In conclusion, this study proposes a method to optimize *in vivo* PBPK parameters in hepatic uptake transporter-mediated DDIs.