Construction of a physiologically-based pharmacokinetic model of coproporphyrin I, a putative endogenous probe for hepatic OATP1Bs and MRP2

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[Background] Coproporphyrin I (CP-I) is a substrate for organic anion transporting polypeptide 1Bs (OATP1Bs) and multidrug resistance-associated protein 2 (MRP2) by in vitro experiments. Plasma CP-I is proposed as an endogenous biomarker for OATP1B-mediated drug-drug interaction (DDI) in clinical studies. In this study, we aimed to establish a physiologically-based pharmacokinetic (PBPK) model for CP-I to account for the dose-dependent effect of rifampicin on the blood concentration-time profiles of CP-I.

[Methods] A PBPK model for CP-I was constructed by introducing a parameter for CP-I biosynthesis (ν_b) to our basic model. Parameters for intrinsic processes in hepatic elimination of CP-I were determined using plated human hepatocytes. To simulate dynamic change in the blood concentration of CP-I by rifampicin, the in vivo inhibition constant for hepatic OATP1Bs (K_i,u,OATP1B: 0.23 μM), determined from DDI cases with pitavastatin, and that for MRP2 (K_i,u,MRP2: 3.5 μM), calculated based on the change in the in vivo biliary clearance of positron emission tomography probe ([11C]-TIC-Me), were initially set.

[Results] We set the ν_b and the hepatic intrinsic clearance (CL_i,u,OATP1B) to reproduce the steady-state blood concentration of CP-I in the control data. Sensitivity analyses showed that blood concentration-time profiles of CP-I with rifampicin were well reproduced by modifying the K_i,u,OATP1B to half of its initial value. Our in vitro experiments using OATP1B-expressing cells showed that the in vitro K_i,u,OATP1B (1.0 μM) and K_i,u,OATP1B (0.23 μM) for CP-I by rifampicin tend to be smaller than those for statins (K_i,u,OATP1B: 1.2-2.9 μM, K_i,u,OATP1B: 0.34-0.86 μM).

[Conclusions] The PBPK model for CP-I was successfully constructed according to in vivo information and in vitro experimental data. Recently, Barnett et al. evaluated CP-I as an endogenous probe for OATP1Bs using nonlinear mixed-effect modeling. Our PBPK modeling approach further enables mechanistic understanding of CP-I pharmacokinetics and separated evaluation of complex effects on hepatic uptake and efflux transporters by DDIs.

2) Takehara et al., under revision
5) Barnett et al., Clin Pharmacol Ther., in press