Physiologically Based Pharmacokinetic Modeling of Rosuvastatin and Prediction of Transporter-Mediated Drug-Drug Interactions Involving Gemfibrozil

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Objectives: Rosuvastatin (Crestor®) may be coprescribed with gemfibrozil due to their complementary lipid-lowering effects. Rosuvastatin is a substrate of OATP1B1, OATP1B3, OATP2B1, NTCP and BCRP transporters. Gemfibrozil inhibits OATP1B1, which accounts for ~50% of the active liver uptake clearance of rosuvastatin. Coadministration of statins and gemfibrozil is associated with an increased risk of myopathy and rare but life-threatening rhabdomyolysis. Patients with genetic polymorphisms of OATP1B1 may be at high risk of severe DDIs when rosuvastatin and gemfibrozil are coprescribed. The objective of this study was to develop a PBPK model of rosuvastatin and to predict tDDIs with gemfibrozil.

Methods: A mechanistic absorption/PBPK model for rosuvastatin was built in the GastroPlus™ 9.0 (Simulations Plus, Inc.). In vitro and clinical profiles were obtained from literature. The permeability-limited liver model included clearances involving sinusoidal uptake, passive diffusional, metabolic, and biliary mediated by canalicular efflux. BCRP-mediated intestinal efflux and EHC were incorporated in the model. The model was validated across several different dose levels following single and multiple oral administrations of rosuvastatin. OATP1B1 tDDIs were predicted through dynamic simulations using the validated PBPK models.

Results: The model adequately predicted hepatobiliary disposition of rosuvastatin. The predicted AUC₀-t, Cmax, and tmax values were within 2-fold of the observed data of rosuvastatin. The predicted increase in AUC₀-t and Cmax of rosuvastatin in the presence of gemfibrozil was ~2-fold which was in close agreement with observed values [1].

Conclusions: The absorption and pharmacokinetics of rosuvastatin were accurately predicted using only in vitro data. The model successfully predicted tDDIs between rosuvastatin and gemfibrozil. This model can be extended for quantitative prediction of the impact of genetic polymorphisms and tDDIs by OATP and BCRP inhibitors. The proposed model can help to identify populations with increased risk of side effects and to optimize their dosing regimen for safe treatment with rosuvastatin.

References: