Application of the extended clearance concept classification system (ECCCS) to predict the victim drug-drug interaction potential of statins

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During drug development, it is an important safety factor to identify the potential of new molecular entities to become a victim of drug-drug interactions (DDIs). In preclinical development, however, anticipation of clinical DDIs remains challenging due to the lack of in vivo human pharmacokinetic data. We applied a recently developed in vitro-in vivo extrapolation method, including hepatic metabolism and transport processes, herein referred to as the Extended Clearance Concept Classification System (ECCCS). The human hepatic clearances and the victim DDI potentials were predicted for atorvastatin, cerivastatin, fluvastatin, lovastatin acid, pitavastatin, pravastatin, rosuvastatin, and simvastatin acid. Hepatic statin clearances were well-predicted by the ECCCS with six out of eight clearances projected within a two-fold deviation to reported values. In addition, worst-case DDI predictions were projected for each statin. Based on the ECCCS class assignment (4 classes), the mechanistic interplay of metabolic and transport processes, resulting in different DDI risks, was well-reflected by our model. Furthermore, predictions of clinically observed statins DDIs in combination with relevant perpetrator drugs showed good quantitative correlations with clinical observations. The ECCCS represents a powerful tool to anticipate the DDI potential of victim drugs based on in vitro drug metabolism and transport data.
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