Assessing the Risk of Drug-Induced Cholestasis Using Unbound Intrahepatic Concentrations

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Author(s) Riede, Julia; Poller, Birk; Huwyler, Jörg; Camenisch, Gian
Author(s) at UniBasel Huwyler, Jörg ;
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Inhibition of the bile salt export pump (BSEP) has been recognized as a key factor in the development of drug-induced cholestasis (DIC). The risk of DIC in humans has been previously assessed using in vitro BSEP inhibition data (IC50) and unbound systemic drug exposure under assumption of the ”free drug hypothesis.” This concept, however, is unlikely valid, as unbound intrahepatic drug concentrations are affected by active transport and metabolism. To investigate this hypothesis, we experimentally determined the in vitro liver-to-blood partition coefficients (Kp(uu)) for 18 drug compounds using the hepatic extended clearance model (ECM). In vitro-in vivo translatability of Kp(uu) values was verified for a subset of compounds in rat. Consequently, unbound intrahepatic concentrations were calculated from clinical exposure (systemic and hepatic inlet) and measured Kp(uu) data. Using these values, corresponding safety margins against BSEP IC50 values were determined and compared with the clinical incidence of DIC. Depending on the ECM class of a drug, in vitro Kp(uu) values deviated up to 14-fold from unity, and unbound intrahepatic concentrations were affected accordingly. The use of in vitro Kp(uu)-based safety margins allowed separation of clinical cholestasis frequency into three classes (no cholestasis, cholestasis in <= 2%, and cholestasis in > 2% of subjects) for 17 out of 18 compounds. This assessment was significantly superior compared with using unbound extracellular concentrations as a surrogate for intrahepatic concentrations. Furthermore, the assessment of Kp(uu) according to ECM provides useful guidance for the quantitative evaluation of genetic and physiologic risk factors for the development of cholestasis.

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