Is it Necessary to Measure Intracellular Unbound Fraction of Inhibitors to Predict Hepatic Efflux Transporter-mediated Drug Interactions?

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Inhibition of hepatic drug or bile acid efflux transporters due to drug interactions (DIs) may have significant toxicological implications. Currently, efflux transporter-mediated DIs are predicted based on the IC₅₀ value and the total maximum plasma concentration (C_max). The robustness of this method is limited by the use of C_max or total cellular concentration rather than unbound cellular (preferably cytosolic) concentration of inhibitors. Further studies are needed to elucidate how critical it is to measure the intracellular unbound fraction of inhibitors (fᵤ,cell,inhibitor). The objective of the current work was to quantitatively assess the impact of different inhibitors exhibiting a range of fᵤ,cell,inhibitor values on the prediction of hepatobiliary disposition of taurocholic acid (TCA), a prototypical bile acid. Cellular total TCA concentrations (Cₜ,Cells) were simulated based on pharmacokinetic parameters estimated from human sandwich-cultured hepatocytes. Simulations were performed using different ([I]ₜ,cell,IC₅₀) values, where [I]ₜ,cell is the total cellular concentration of inhibitor and IC₅₀ represents the inhibitory potency against efflux transporters. For each ([I]ₜ,cell,IC₅₀) scenario, simulated Cₜ,Cells were compared when fᵤ,cell,inhibitor was equal to 1 vs. 0.02. Simulations demonstrated that when ([I]ₜ,cell,IC₅₀) was >1, a decrease in fᵤ,cell,inhibitor from 1 to 0.02 resulted in a >2-fold increase in Cₜ,Cells of TCA. For this scenario where ([I]ₜ,cell,IC₅₀) >1, hepatic exposure of TCA was sensitive to fᵤ,cell,inhibitor, indicating the importance of measuring fᵤ,cell,inhibitor in cells or cytosol to accurately predict altered disposition of TCA. However, the difference in Cₜ,Cells due to varying fᵤ,cell,inhibitor decreased to <2-fold when ([I]ₜ,cell,IC₅₀) was >80. These simulation results were validated by three model inhibitors: telmisartan, bosentan, and troglitazone-sulfate. In conclusion, the impact of variability in fᵤ,cell,inhibitor values on the hepatobiliary disposition of TCA depends on the ([I]ₜ,cell,IC₅₀) value for inhibitors. This information may be useful in guiding future studies.