Liver Safety Comparison of Two Treatments for Autosomal-Dominant Polycystic Kidney Disease (ADPKD) Using Quantitative Systems Toxicology Software (DILIsym)

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PURPOSE
Lixivaptan, a vasopressin-2 receptor antagonist, is being developed for the treatment of autosomal-dominant polycystic kidney disease (ADPKD), an orphan disease that is an unmet medical need. We prospectively compared the potential for lixivaptan to cause liver toxicity to another drug in the same class, tolvaptan, which has produced off-target liver signals in clinical trials (1).

OBJECTIVE
The main objective of this research was to determine if a next-in-class compound would provide a better liver safety profile than the first-in-class comparator drug for treatment of an important unmet medical need, ADPKD.

METHOD
In vitro data relating to reactive oxygen species formation, mitochondrial toxicity, and bile acid transporter inhibition for lixivaptan and its metabolites were collected. Using these data, lixivaptan and its metabolites were represented in DILIsym, QST software for predicting drug-induced liver injury. Lixivaptan PBPK model was also represented within DILIsym, incorporating clinical trial PK data. Proposed ADPKD treatment dosing regimens were simulated and compared to previously published DILIsym simulations of tolvaptan (1).

RESULTS
In Vitro Results
In vitro experiments measured mitochondrial dysfunction, ROS generation, and bile acid transporter inhibition due to all four chemical species. For the mitochondrial assay and the ROS assay, a parallel culture was run in order to assess the intracellular concentration present in each assay; the assay results were corrected for these concentrations before the parameter values were calculated.

PBPK Representation
The PBPK representation for lixivaptan and its major metabolites was constructed using clinical data for optimization and validation. The clinical trials used were Phase I trial data (n = 67) for seven-day 100 mg BID and 400 mg BID dosing regimens. The simulation results reasonably matched the data. Liver accumulation data from rat WBAR study and from in vitro studies collected for the work were consistent with simulated liver concentrations.

DILIsym Simulation Results
Simulations predicted lixivaptan to be less toxic than tolvaptan; while tolvaptan had significant ALT elevations in its SimPops simulation, lixivaptan had only sub-clinical ALT elevations. Simulations for lixivaptan suggested a low rate of ALT elevations at 400 mg BID, which suggests that the simulation results may be slightly conservative. ROS inhibition was found to be the main mechanism responsible for simulated ALT elevations at the supratherapeutic dose of 400 mg BID, which is consistent with the findings of previous studies in which bile acid accumulation and ETC inhibition were found to be the mechanisms of toxicity (1).

DILIsym Parameter Input Comparison

CONCLUSIONS
Lixivaptan was predicted to be safer than tolvaptan with respect to the liver toxicity mechanisms represented in DILIsym. Quantitative and qualitative differences were identified between the two drugs. These findings paved the way for confirmatory clinical trials with lixivaptan in ADPKD.

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