IVIVE to Facilitate Animal-free Risk Assessment of Potential Developmental Toxicants

X. Chang[1]*, J. Palmer[2], E. Donley[2], E. Reinke[1], D. Allen[1], and N. Kleinstreuer[3]

[1]Inotiv, RTP, NC, United States; [2]Stemina Biomarker Discovery Inc., Cambridge, MA, United States; and [3]NIH/NIEHS/DTT/NICEATM, RTP, NC, United States

Background and Purpose

In vitro human cell-based methods can be applied to toxicity screening in a faster, cost-effective, and more human-relevant manner than animal tests. They can also inform safe exposure levels when combined with in vitro to in vivo extrapolation (IVIVE). IVIVE uses pharmacokinetic (PK) models to relate chemical-specific in vitro activity concentrations to in vivo exposure levels that could result in adverse effects in humans or laboratory animals. Our primary goal was to evaluate if data from a human induced pluripotent stem cell (iPSC)-based assay, devTOXqP, in combination with IVIVE, can be used to predict in vivo lowest-observed-effect-level (LOEL) for potential developmental toxicants.

Methods

We selected 186 chemicals with in vivo embryo-fetal development data and tested them in the devTOXqP assay. We derived a developmental toxicity potential (dTP) concentration for each chemical and performed IVIVE to translate the dTP concentration to a corresponding equivalent administered dose (EAD). The EADs were than compared with the LOEL in rat developmental toxicity studies, as well as human clinical data and minimal risk levels, depending on data availability. To evaluate the impact of in vitro kinetics on EAD estimates, an equilibrium distribution model was applied to translate dTP concentrations to free medium concentrations before subsequent IVIVE analyses. To identify the optimal approach, we generated EADs with several PK models, including both open-source and commercial physiologically based pharmacokinetic (PBPK) models. The root mean squared error between EADs and in vivo LOELs across all tested chemicals were calculated and compared to evaluate the overall performance of a PK model. We identified modeling approaches that provided the lowest EADs, i.e., the most conservative estimates of safe exposure, and those with the most accurate predictions for rat developmental toxicity LOELs.

Results

The estimated free medium concentration was lower than nominal concentration. Thus, using the free medium concentration of a chemical in IVIVE analysis produced a lower EAD than those obtained using the nominal concentration for the same chemical. Across models, EADs generated using free medium concentration were lower than rat LOELs for >80% of chemicals, suggesting that the devTOXqP assay may provide more conservative estimates for use in risk assessment than rat toxicity studies. On the other hand, EADs generated using the nominal dTP concentration appeared to provide more accurate predictions of in vivo LOELs overall. This suggested that use purpose (e.g., risk assessment versus LOEL estimation) needs to be considered when determining the optimal IVIVE approach for a chemical. Further investigation on factors affecting the performance of IVIVE would be necessary.

Conclusions

The devTOXqP assay in combination with IVIVE approaches can predict rat developmental toxicity effect levels with reasonable accuracy in a high-throughput format. This further supports the utility of IVIVE with using mechanistically relevant in vitro assay data to quantitatively assess a chemical's developmental toxicity potential. This project was funded in whole or in part with federal funds from the NIEHS, NIH under Contract No. HHSN273201500010C.

Keywords: In Vitro and Alternatives, Pharmacokinetics, Reproductive and Developmental Toxicology