PBPK Modeling to Predict Chemical Distribution in Brain and Adipose Tissues

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Background and Purpose

To facilitate decision-making in drug discovery and risk assessment, physiologically based pharmacokinetic (PBPK) modeling is used for high-throughput applications. PBPK models are based on various assumptions and simplifications to make them computationally tractable. High-throughput PBPK may use a standardized (chemical-independent) description of physiology. Most existing high-throughput, open-source PBPK models predict chemical concentrations in major body compartments such as the liver, kidney, and gut. However, estimates for additional organs require specialized models. As an example, for neurotoxicity evaluations, chemical concentrations in the brain depends upon interactions with the blood-brain barrier. Incorporating the blood-brain barrier in a PBPK model and evaluating whether a chemical can cross this barrier is an important step in assessing the potential neurotoxicity of the chemical. Another limitation of existing open-source PBPK models is that they often do not include an explicit adipose tissue compartment. Adipose tissue plays a critical role in toxicokinetics by acting as a storage compartment for lipophilic chemicals and a source of continuous internal exposure as the chemical is released. In this study, we added brain and adipose tissue compartments to the existing generic PBPK model from the U.S. Environmental Protection Agency's (EPA's) httk R package (v2.2.2) to better estimate chemical concentrations in these two toxicologically relevant compartments.

Methods

We executed the workflow in three stages, starting with the identification of model structure, the required ordinary differential equations, and the model parameters. We then developed required files and functions using different simulation packages and programming software. Finally, we tested the compiled model results to validate the concentration–time profile predictions in the two tissue compartments of interest. We are applying the initial process, created using a perfusion-limited model, to revise the model with a complex brain compartment that incorporates the blood-brain barrier.

Results

Concentration–time profiles generated by the model were compared with in vivo data. Both hydrophilic chemicals like acetaminophen and pravastatin and lipophilic chemicals like mono(2-ethylhexyl) phthalate, dieldrin and bisphenol A were studied. Accumulation was observed for lipophilic substances in adipose and brain compartment but not for hydrophilic substances. Predicted brain and adipose Cmax (maximum concentration) from the model were within 2-fold of the experimental data for acetaminophen and dieldrin. The corresponding Tmax (peak times)

predicted from the model were also similar to the experimental Tmax for both chemicals. The predicted brain Cmax between our model and the commercial Simcyp PBPK model fell within 10-fold of one another for 92 chemicals with potential developmental neurotoxicity. This alignment between the model's predictions against predictions from commercial models, as well as experimental data, signifies the robustness of the PBPK model and its applicability in various aspects of drug development.

Conclusions

Chemical distribution in specific, toxicologically relevant body compartments such as the brain and adipose tissue can be quantified by expanding existing high-throughput PBPK modeling approaches.

Evaluations of drug efficacy and safety, particularly in the treatment of neurological disorders and psychiatric conditions, can be supported through predictions of chemical concentrations in the brain tissue. The brain compartment predictions not only help in optimizing drug dosages but also assists in assessing potential neurotoxicity. Implementing blood-brain barrier activity can aid in predicting the brain tissue influx and efflux of chemicals from capillary blood as a diffusion-limited process and having a brain compartment PBPK model with a blood-brain barrier allows researchers to more accurately assess how drugs penetrate this barrier than using a simple perfusion-limited model, enabling the development of medications tailored to treat neurological disorders and brain-related conditions.

Incorporation of an adipose compartment in the PBPK model can provide valuable information on the biological propensity for chemical bioaccumulation as well as play a vital role in assessing the potential risks associated with lipophilic drug compounds and the impact of obesity on drug pharmacokinetics. The integration of brain and adipose compartment PBPK models can undoubtedly play a pivotal role in improving drug development and clinical decision-making.
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