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Physiologically Based Pharmacokinetic (PBPK) Modeling

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Over the past few decades, drug research programs have used a variety of computer models. Drug disposition modeling and simulation have emerged as essential tools in drug research, clinical study design, and regulatory assessment. Publications and regulatory filings related to physiologically based pharmacokinetic (PBPK) modeling have increased significantly in recent years [1]. To provide a mechanistic representation of the drug in biological systems, PBPK models integrate data on the drug with separate previous knowledge on the biology and physiology at the organism level. This enables the a priori modeling of drug concentration–time profile.

These models include highly complicated frameworks that incorporate anatomical and physiological data, as well as empirical and semi-mechanistic methodologies. The benefit of PBPK modeling is that it can simulate various physiologies across different age groups.

How is a PBPK model built? The organs that are most important to the drug's absorption, distribution, excretion, and metabolism, their physiological/pharmacological function, or volumes are explicitly represented in a PBPK model. Usually, these include the gonads, thymus, adipose tissue, muscle, bone, skin, stomach, spleen, pancreas, gut, liver, kidney, brain, lungs, and stomach. The arterial and venous blood compartments connect the tissues, and each one has its own permeability, tissue-partition coefficient, volume, and blood flow rate. Such information is typically found in the database of the PBPK software that is available when specialized software packages are utilized.

The creation of a number of commercial platforms that incorporate physiological databases and apply PBPK modeling techniques, including GastroPlus (Simulations Plus, Lancaster, PA), SimCyp (SimCyp, Sheffield, UK), and PKSim and MoBi (Bayer Technology Services, Leverkusen, Germany), has recently made it easier to use sophisticated full-blown PBPK models. Extrapolations to new clinical situations, such as distinct treatment regimens or patient subgroups are a crucial use of PBPK models.

The applications of the models include

- Pediatric extrapolations, where, with the support of the US Food and Drug Administration, a reference PBPK model for an adult population, is scaled to specific life stages in children.
- Extrapolations to diseased populations, such as those with cirrhosis or hepatically compro mised liver disease.
- Assessing potential drug-drug interactions (DDI), such as by taking competitive inhibition of a metabolizing enzyme into account.
- Simulating particular dosing schemes to scale between various treatments scenarios.

- Changing the relevant compound/formulation parameters to evaluate the effects of various medication formulations.
- Cross-species extrapolation is one of the advanced applications [2].

To sum up, PBPK models can be a useful tool for drug development, especially when it comes to the ability to create a priori simulations. Consequently, pharmaceutical corporations and regulatory bodies such as the US Food and Drug Administration are using them more and more.

Prospects for PBPK evaluation in the future to evaluate a) drug-drug interactions mediated by drug transporters or drug metabolizing enzymes, drug exposure in patients with renal and/or hepatic organ impairment, b) dosing regimen prediction, sampling timepoint selection, and dose validation in pediatric patients from newborns to adolescents, d) maternal-fetal drug disposition during pregnancy and e) pH-mediated drug-drug interactions in patients treated with proton pump inhibitors are valuable [3].

With the increasing complexity of diseases and the growing need for individualized therapy, PBPK modeling is essential, and we have to put an effort into building our expert scientific personnel in this field in the coming days.

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