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RESEARCH ARTICLE

The Perks and Drawbacks of Physiologically-Based Pharmacokinetic Modeling

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ABSTRACT
Physiologically-based pharmacokinetic (PBPK) models use a mechanistic approach to integrate physiological parameters, physicochemical drug properties, and biochemical processes by means of mathematical equations to predict the concentration of a drug over time in blood and tissues. These models represent a robust tool for the pharmaceutical sciences, but also applications in chemical risk assessment for drugs and chemicals of forensic interest or in occupational hazards have been explored over the last decade. Much like other computational tools, PBPK models' application face challenges concerning validity, transparency and lack of collaboration between professionals in different fields. The potential uses and challenges of PBPK modeling are discussed, as well as some ways to address the latter.

Editorial

Physiologically-based pharmacokinetic (PBPK) models are a widely used tool in pharmaceutical sciences. These models use a mechanistic approach to integrate physiological parameters, physicochemical drug properties, and biochemical processes by means of mathematical equations to predict the concentration of a drug over time in blood and tissues[1]. A certain level of accuracy can be attributed to these models since they are based on the physiological and biochemical properties of real tissues instead of conceptual compartments as the ones proposed for classical pharmacokinetic models. Furthermore, specific population characteristics can be integrated into the models such as age, sex, weight, body composition, organ functions, genetics, among others; this in turn represents the possibility of a certain degree of customized predictions. However, with great predictive robustness comes great complexity; and in designing PBPK models, developers must often face the dilemma between physiological fidelity and model parsimony, hence, some assumptions must be made (e.g., the lymph system is rarely included in most PBPK models)[2,3].

The power to estimate drug concentrations in specific tissues implies the assurance of drug availability for target organs, and thus, a potential way of relating plasmatic concentrations with a pharmacological effect[4]. Pharmacokinetic (PK) parameter calculations through PBPK simulation can also be used for dosing optimization and safety margins predictions[5,6]. These models are potentially useful in drug-drug interaction (DDI), pediatric and special population studies representing a cost-effective tool that addresses of some ethical challenges associated with clinical trials in sensitive populations (e.g., pregnant women, organ transplant patients, etc) and potentially useful for drugs with a narrow therapeutic window[6–12]. Aside from the pharmacological scope, PBPK models represent a safe tool for studying substances with little or no therapeutical value that are rarely submitted to clinical studies, such as drugs of abuse or toxic occupational chemicals; hence they can be used for forensic and/or regulatory purposes[13–16].

The building of a PBPK model is an iterative process including data collection, mathematical representation, parametrization, extrapolation and verification with *in vitro* and *in vivo* data, modification, validation and constant evaluation for better predictions. PBPK models are often developed using animal data since preclinical studies can provide information that is not usually attainable in clinical trials. Unlike simple allometry and its limitations for extrapolation due to differences in exposure routes, physiology (e.g., metabolic clearance) and biochemical processes, PBPK models provide a robust approach to conduct extrapolations across species by incorporating the variability in said conditions[17,18]. However, *in silico* predictions are as good as their comparability with reality, and so we face one of the most challenging aspects of PBPK modelling: validation. While physiological parameters databases are available and standard pharmaceutical practices ensure that drug PK parameters are reported, tissue drug concentration data or profiles are not usually published, and thus, the confidence in a model based on tissues begins to shake.

A couple of ways in which we can address this issue come to mind: a) bigger efforts in the scientific community in obtaining and sharing information, and b) the ever-promising developing technology; and both imply a considerable investment. Preclinical and clinical trials have been subjected to substantial standardization especially focusing on the reporting of PK parameters, and this task alone is economically and time-costly; however, tissue-specific data in PK studies and its incorporation into a harmonized database could lead to better model validations, especially for DDI predictions. This is not an unusual proposal, just two years ago a database for PK data and parameters for environmental chemicals was published[19]. As for technology, the novel Organ-on-a-chip (OoC) use in simulating *in vivo* environments *in vitro* as an alternative for animal testing could also mean better chances at having tissue concentration data for model validation[20]; however, despite progress, complexity in organ function representation is far from perfected[21].

PBPK modeling is no simple task, it requires computational power for simultaneous solutions of complicated mathematical equations, and so software and computing platforms for modelers have become a faster way to build models. While some commercial software may be user-friendly, there is a considerable lack in coding transparency; coded models are either not accessible or untransferable to other platforms[22,23]. On the other hand, more transparent software lacks usability for non-programmers. Several efforts have been made to address this issue, from translational research initiatives to the creation of guidelines in reporting PBPK models by several regulatory agencies[24–28]. Collaboration between the computational modeling and the scientific communities is key in overcoming

this challenge; hence we must also approach this issue from an academic scope. Few undergraduate programs offer a curriculum that includes PBPK modeling and application, most of the training in PBPK is offered in graduate or software training programs. This does not only reduce the number of work groups in PBPK research in academia, but indirectly generates a shortage of reviewers with sufficient expertise and experience to assess the validity of conclusions drawn from models submitted for publishing or application in risk assessment[29,30].

Conclusions

The appeal of computational tools, such as PBPK models, is noticeable; the variety of applications from drug development to forensic toxicology interpretations is potentially beneficial for public health; however, many obstacles remain to be overcome to exploit their full potential. This is an invitation to the readers to reflect on the ways we can contribute to the challenges presented above, whether it is publishing in open access journals supplementary materials with data that could help model validation, proposing research projects that include new technology or the development of open databases, collaborating in the development of open-source software, or promoting professional training in the subject.

Conflicts of interest statement

The author has no conflicts of interest to declare.

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