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ARTICLE

Increasing application of pediatric physiologically based pharmacokinetic models across academic and industry organizations

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Abstract

There has been a significant increase in the use of physiologically based pharmacokinetic (PBPK) models during the past 20 years, especially for pediatrics. The aim of this study was to give a detailed overview of the growth and areas of application of pediatric PBPK (P-PBPK) models. A total of 181 publications and publicly available regulatory reviews were identified and categorized according to year, author affiliation, platform, and primary application of the P-PBPK model (in clinical settings, drug development or to advance pediatric model development in general). Secondary application areas, including dose selection, biologics, and drug interactions, were also assessed. The growth rate for P-PBPK modeling increased 33-fold between 2005 and 2020; this was mainly attributed to growth in clinical and drug development applications. For primary applications, 50% of articles were classified under clinical, 18% under drug development, and 33% under model development. The most common secondary applications were dose selection (75% drug development), pharmacokinetic prediction and covariate identification (47% clinical), and model parameter identification (68% model development), respectively. Although population PK modeling remains the mainstay of approaches supporting pediatric drug development, the data presented here demonstrate the widespread application of P-PBPK models in both drug development and clinical settings. Although applications for pharmacokinetic and drug–drug interaction predictions in pediatrics is advocated, this approach remains underused in areas such as assessment of pediatric formulations, toxicology, and trial design. The increasing number of publications supporting the development and refinement of the pediatric model parameters can only serve to enhance optimal use of P-PBPK models.

Trevor N. Johnson and Ben G. Small contributed equally to this work.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Application of physiologically based pharmacokinetic (PBPK) modeling in both industry and academia has increased significantly during the past 2 decades. Drug–drug interaction prediction in adults remains the most frequent application of PBPK modeling in drug development.

WHAT QUESTION DID THIS STUDY ADDRESS?

This study assessed the growth of PBPK modeling in pediatrics (P-PBPK) in clinical, drug, and model development settings.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Pediatric PBPK models are being used increasingly to leverage existing knowledge to allow a more mechanistic approach to inform dose selection (e.g., small and large molecules) and formulation bridging, extrapolate drug–drug interactions, and identify knowledge gaps.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

Our findings demonstrate that both independent and ideally collaborative efforts by model providers, academia, and industry and regulatory authorities are required to continue to advocate the application of pediatric PBPK models, especially in drug development.

INTRODUCTION

Historically, the development and use of physiologically based pharmacokinetic (PBPK) models was initially focused on toxicology and prediction of exposure to chemicals and environmental substances.[1] However, in recent years, there has been a rapid rise in their application in clinical pharmacology, particularly in drug development.[2] In parallel with this move from scientific curiosity to ingrained industrial application has been the associated increase in regulatory acceptance of PBPK modeling in lieu of clinical studies and to inform the drug label, mainly for drug–drug interactions (DDIs).[3] A recent publication[4] indicated that the rate of growth of PBPK publications in peer-reviewed journals from 2000 to 2019 was more than 40-fold, which was much greater than for general pharmacokinetic (PK) modeling (less than threefold). The most common areas of application were study design, predicting formulation effects, and metabolic DDIs.

One of the advantages of PBPK models is that they make optimal use of available data by marrying the complex interplay of physiological parameters with drug characteristics, thus representing a mechanistic approach to predict the PK of drugs in different populations, including pediatrics. Pediatric PBPK (P-PBPK) models integrate additional information regarding organ development and ontogeny of pathways involved in drug disposition[5] and are frequently used for dose projection in different age groups based on equivalent adult exposure in both clinical and drug development settings.[6] An increasing number of examples of the application of P-PBPK models to replace or inform studies in the pediatric population is beginning to emerge.[7,8] Although the increase is reflected in publications from global regulators, the number of drug submissions that includes P-PBPK modeling remains relatively small. Of the regulatory submissions assessed by the US Food and Drug Administration (FDA) in 2018 and 2019, 9% included P-PBPK modeling, and for the Pharmaceutical and Medicines Device Agency, it was 5%.[9,10]

Legislation in both the United States (Pediatric Research Equity and Best Pharmaceuticals for Children Acts) and European Union (Pediatric Regulation) has been introduced to mandate pediatric drug development by offering a 6-month patent extension in return for conducting pediatric studies as discussed by Rose.[11] These are described in a pediatric study plan (PSP; United States) or pediatric investigation plan (PIP; European Union) and are submitted to regulators early in the drug development process. These development plans are aimed at ensuring that relevant data are obtained in pediatric clinical studies to support the authorization of a medicine for children. Model-informed drug development (MIDD), inclusive of PBPK modeling, is often applied to address the unique challenges associated with the conduct of pediatric trials, which include a small number of patients, variability in physiological characteristics, uncertainties in dose selection, and ethical complexities.[12] Efforts by academic groups and the pharmaceutical industry to verify the mechanistic P-PBPK models as well as generate the robust data required to populate the models have also increased.[5]

Thus, the number of publications on the application of PBPK modeling for pediatrics in both industry and academia has exploded in recent years.

The primary aim of this article is to give a detailed overview of the growth and areas of application of P-PBPK models to date in clinical and drug development settings, and in advancing pediatric model development in general. In each category, specific applications will be explored with a view to highlighting areas where the utility of P-PBPK models is well supported or where additional research may be required moving forward.

METHODS

Data set construction and verification

Two independent approaches were used to identify publications relating to the application of P-PBPK models. This was done to ensure that all available and relevant publications were captured for the analysis (Figure 1). First, an in-house curated data set (ICD) of articles from peer-reviewed journals collected on a month-to-month basis by the Simcyp Library team since 2003 and up to June 29, 2021, related to the field of PBPK models was organized by listing and categorizing its member articles into the following fields: PubMed Identifier (PMID), first author, year, title, modeling software used, rejection code and primary and secondary applications, research group affiliation, and origination from either an academic or commercial software provider or regulatory or pharmaceutical industry environments. Starting from the assumption that all articles were valid for the intended purpose of this analysis, rejection criteria (rejection codes) were applied to discriminate articles not meeting the requirement of having substantial content related to the application of P-PBPK models. The rejection criteria were the following: not pediatric PBPK (adult only; code N), fetal or pregnancy PBPK (code F), experimental (e.g., ontogeny study but no P-PBPK application; code E), literature reviews /tutorials/commentaries/letters/editorials (code R), thesis (code T), poster/book/unpublished (code P), not PBPK (e.g., pediatic population PK [POP-PK]; code X). Second, an additional broad search of PubMed (National Center for Biotechnology Information, National Institutes of Health) was conducted up to and including June 29, 2021, using the following search terms: ((*Paediatric* OR *Pediatric*) AND (*Pharmacokinetics*) AND (*PBPK* OR *Physiologically based pharmacokinetic*) AND (*modelling* OR *modeling*)) AND (*"Physiologically-Based Pharmacokinetic"* [*Title*] OR *"PBPK"* [*Title*]). This resulted in the identification of 160 studies, which after classification and scrutiny, 35 additional studies were considered relevant. The ICD was

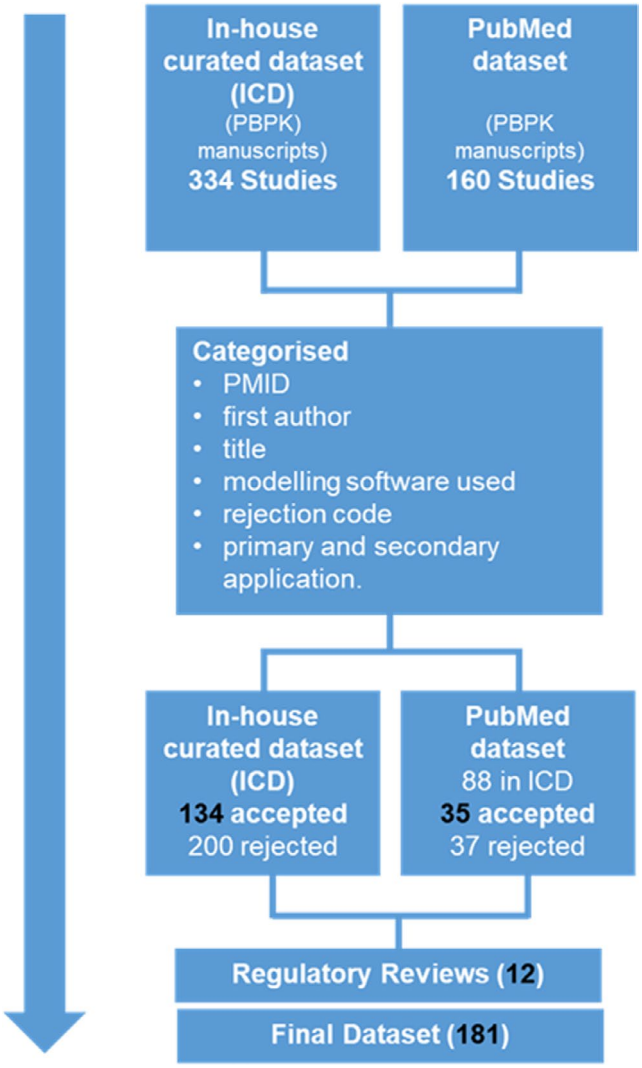

FIGURE 1 Workflow describing generation of the final data set used for the analysis conducted in this article. ICD, in-house curated data set; PBPK, physiologically based pharmacokinetic; PMID, PubMed Identifier

further bolstered by the addition of clinical pharmacology reviews from a regulator (FDA) captured between 2018 and 2020 (inclusive) where P-PBPK modeling had been used but the study was not otherwise published.

Article classifications

From the final data set, articles were carefully evaluated and sifted manually by two independent operatives and assigned primary and secondary applications. In cases of mismatch, these were discussed by all authors before final assignment. For some of the applications where there was overlap (e.g., those primarily and secondarily classified as drug development and biologics, respectively, which may

also be related to dose selection), these cases were classified based on the major focus of the research.

Each article was set to one of three primary application areas (Table 1). The first related to the use of the P-PBPK model to predict clinical data for approved drugs; specific examples include providing insight into PK covariates or optimizing doses. The second application indicated support of a drug in development. The final application area related to studies where the nature of the research was to generate or refine systems data for the pediatric model itself. The articles in the three primary applications were then assigned to a secondary application area (Table 1). The final data set (PPBPK_Applications_Final_Dataset.xlsx) in an Excel format is available in the Supplementary Material.

Data analysis

Data analysis was executed using Microsoft Excel (for Microsoft 365, Version 16.01.13801.20722) and R (Version 4.0.5 [R Foundation for Statistical Computing]; Shake and Throw, 64 bit) using the packages dplyr (Version 1.0.5), magrittr (Version 2.0.1), and ggplot2 (Version 3.3.3).

RESULTS

Literature search on P-PBPK applications

Full details of the method workflow are shown in Figure 1; a total of 181 publications/regulatory reviews were included in the final data set.

Growth in use of P-PBPK by research group affiliation

The growth in the number of publications involving P-PBPK during the past 15 years is shown in Figure 2 (data detailed by research group affiliation). Starting from 2005, the number of publications in the early years was limited,

TABLE 1 Primary and secondary applications for classification of articles

Application	Justification
Primary	
Clinical Settings	Studies where approved[a] drugs were being used to predict clinical data with a view to optimizing doses or to explore covariates and provide insight into model verification/performance against observed data
Drug development	Studies where the intended use of the P-PBPK model was part of a PIP or PSP or to gain regulatory approval for an NME/NDE
Model development/evaluation	Studies where research was conducted to generate new systems data or the refinement of existing P-PBPK parameters; the general performance verification of P-PBPK models is included in this category
Secondary	
Biologics	Article has objective/content related to biologics (e.g., mAb disposition)
Drug–drug interaction	Article has objective/content related to drug–drug interaction
Dose selection	Article has objective/content related to dose selection/prediction of exposure
Formulation	Article has objective/content related to formulation
Pharmacokinetics/covariate identification	Article has objective/content related to pharmacokinetics and/or covariate identification
Pharmacodynamics	Article has objective/content related to pharmacodynamics
Population	Article has objective/content related to adding/evaluating population model
Trial design	Article has objective/content related to trial design
Toxicology	Article has objective/content related to toxicology

Abbreviations: mAB, monoclonal antibody; NDE, new drug entity; NME, new molecular entity; PIP, pediatric investigation plan; P-PBPK, pediatric physiologically based pharmacokinetic; PSP, pediatric study.

[a]Not necessarily in the population being studied in the article.

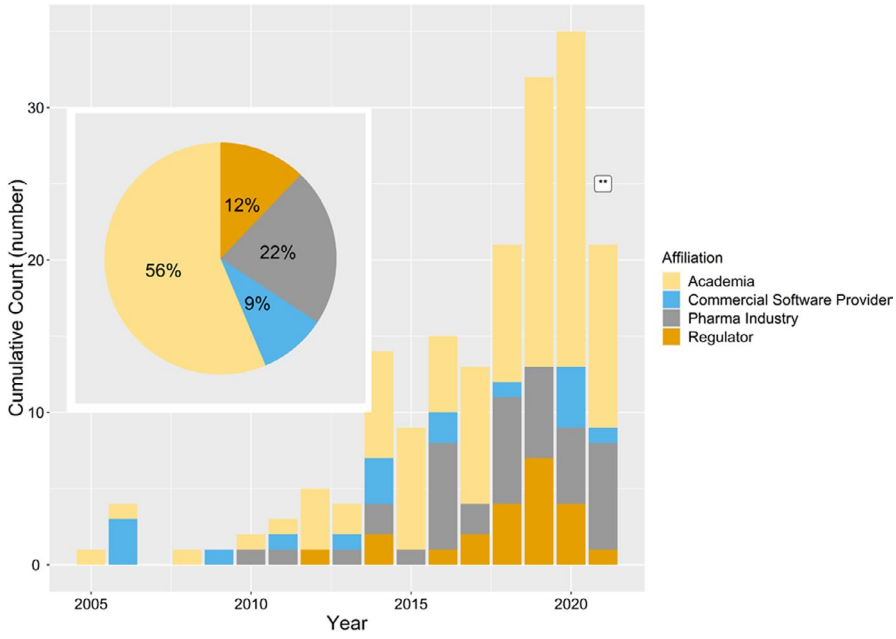

FIGURE 2 Growth in pediatric physiologically based pharmacokinetic studies by affiliation of research group. Stacked bars represent cumulative count (e.g., in 2005 there was one study assigned to academia, and in 2006 there were four studies: three by commercial software providers and one by academia). Inset pie chart shows the percentage of the total data set (absolute numbers: academia, 102; pharma industry, 40; regulator, 22; commercial software provider, 17) in each group. **Partial year recorded

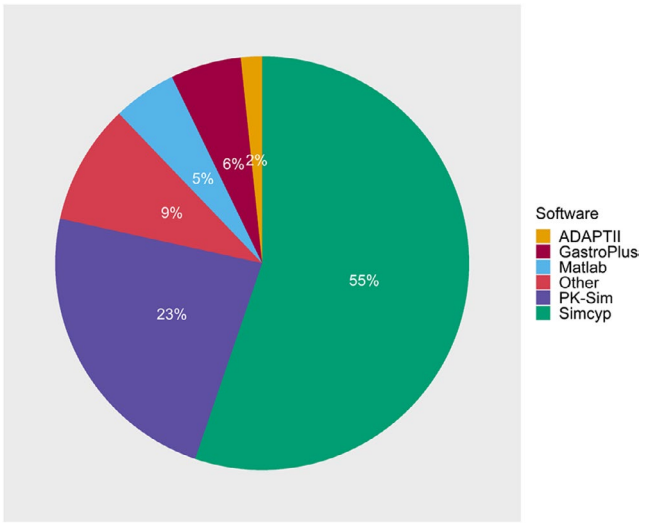

FIGURE 3 Proportions of pediatric physiologically based pharmacokinetic studies using different software

with very little growth up to 2010 followed by a rapid increase in the past decade. From 2005 to the average of the past 2 full years (2019 and 2020), there has been an approximate 33-fold increase. Overall, the largest publication group by research affiliation were academic groups with 56% followed by the pharmaceutical industry with 22%, regulatory 12%, and commercial software provider groups with 9%. Viewing the increase in publications in relation to originating research group affiliation, it is interesting to note that although there was a steep rise in all groups, latterly, an increasing number of contributions came from the pharmaceutical industry and regulatory agencies.

P-PBPK by platform used

P-PBPK models published involving the main commercial and noncommercial software are shown in Figure 3. Although PK-Sim is distributed under a GPLv2 licence, much of the previous development and use of this software falls under the banner of commercial use, hence for the purpose of this study, this software was classified as a "commercial" package. The commercial packages Simcyp (55%) and PK-Sim (23%) were the most frequently used followed by the commercial package GastroPlus (6%), the generic modeling tool MATLAB (5%), and ADAPT11 (2%). Other software included a mix of generic and specialized modeling tools: NONMEM, R, acs1X, and acslXtreme. For the drug development category, all studies used commercial software with 72% using Simcyp, 16% using PK-Sim, and 9% using GastroPlus. For clinical and model development, 83% used commercial software as a percentage of the total in both categories.

P-PBPK by primary and secondary applications

Categorization of the final data set into primary application resulted in 90 (50%) articles in clinical, 59 (33%)

in model development, and 20 in drug development (Figure 4, inset). In addition to the 20 articles in drug development, a further 12 FDA reviews were added to this category, giving a total of 32 (18%); although these are not published per se, they are available in the public domain. There is a clear historical increase in the number of clinical and drug development applications (Figure 4).

The articles in each primary application were then further categorized according to the secondary application of P-PBPK modeling (i.e., biologics; DDIs; dose selection; formulation; pharmacodynamics [PD]; PK, population file development; trial design; toxicology [full definitions are provided in Table 1]). Classification of articles into one of the nine further applications relied on each article having an objective and content related to that category; the results are summarized in Figure 5a–c.

In the clinical primary application, nearly half of the articles involved the use of P-PBPK models for the prediction of PK or to explore PK covariates, for example, protein binding or renal function (47%) followed by dose selection (37%), DDI assessment (7%), toxicology (7%), formulation effects (2%), and PD (1%).

In the drug development primary application, not surprisingly, 75% of the articles/FDA reviews were associated with use of P-PBPK models for dose selection followed by formulation (9%), PD (6%), biologics (6%), and DDI assessment (3%).

Of the 59 articles assigned to the model development primary application, the bulk of them (68%) related to the assessment of population parameters incorporated in the pediatric module. The remaining 32% related to development of P-PBPK models in the areas of formulation, biologics, DDI, trial design, PK, and toxicology. The different secondary applications as the percentage of primary classification can be seen in Figure S1 and are provided in Table S1.

Among the three primary applications, there were a number of interesting case studies demonstrating the versatility of P-PBPK modeling, which are described hereafter.

Case studies demonstrating the broad application of P-PBPK

Drug development

Biologics

Glioblastoma is an aggressive malignancy in both children and adults. Asunercept is an Fc-fusion protein that binds and neutralizes CD95 ligand (CD95L) binding to the Fas pathway. Extrapolation of a qualified adult PBPK[13] model to a pediatric population (1–18 years) was used to determine a starting dose. Bodyweight was found to be a significant covariate in realizing similar pediatric (>12 years) and adult steady-state exposures, with higher doses per kg of bodyweight being required for younger children (1–12 years).

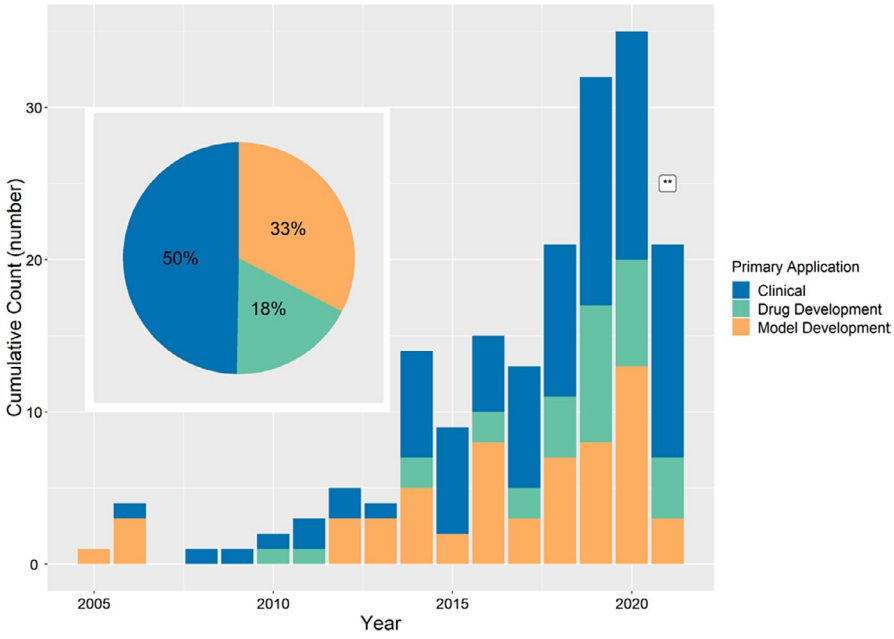

FIGURE 4 Growth in pediatric physiologically based pharmacokinetic by primary application. Stacked bars represent cumulative count (e.g., in 2005 there was one study assigned to model development, and in 2006 there were four studies: one assigned to clinical and three assigned to model development). Inset pie chart shows percentage of the total data set (absolute numbers: clinical 90; drug development, 32; model development, 59) in each primary application. **Partial year recorded

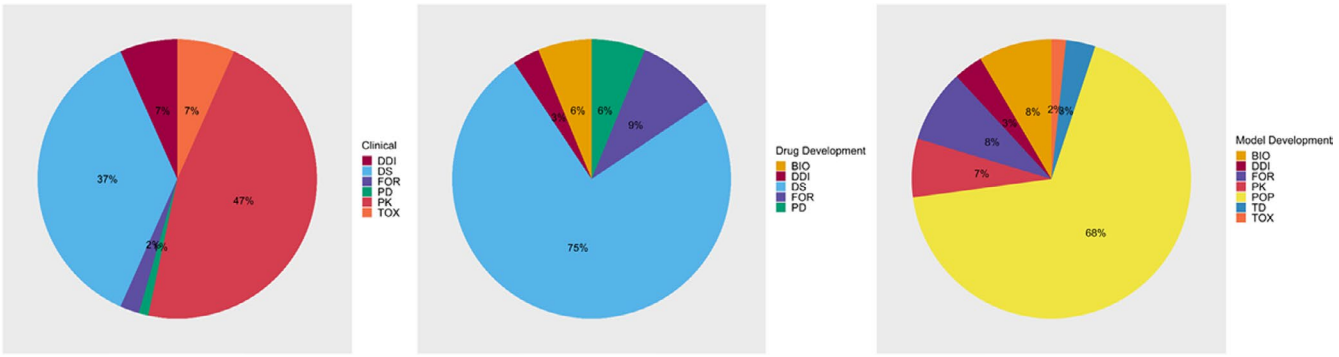

FIGURE 5 Use of pediatric physiologically based pharmacokinetic models by primary application (clinical [$n = 90$; a], drug development [$n = 32$; b], and model development [$n = 59$; c]) and secondary applications. BIO, biologics; DDI, drug–drug interaction; DS, dose selection; FOR, formulation/absorption; PD, pharmacodynamics; PK, pharmacokinetics/covariate identification; POP, population file development; TD, trial design; TOX, toxicology

Pharmacodynamics

Everolimus was evaluated to treat tuberous sclerosis complex-associated treatment refractory partial-onset seizures in infants (<2 years). After qualification of the PBPK model[14] with clinical trial data in adults and older children (>2–18 years), the P-PBPK model was used to extrapolate exposure and efficacy in a younger population (6 months to 2 years) with the P-PBPK model exposures being used to drive the PD models of short-term and long-term efficacy. This example is ultimately about dose selection but with key emphasis on PD; this was decided as the final classification.

Drug–drug interaction

Guanfacine is a nonstimulant treatment for children with attention deficit hyperactivity disorder. Owing to its predominant cytochrome P450 (CYP) 3A4–mediated metabolism, guanfacine exposure may be altered by other concomitant medication to underexpose/overexpose the pediatric target population. An adult PBPK model for guanfacine, validated with clinical data utilizing a CYP3A4 inhibitor and inducer, was used to recommend dose adjustments that appeared in the label for children and adolescents (6–17 years) receiving strong or moderate CYP3A4 inhibitors/inducers.[15]

Model development and evaluation

Population

Cristea et al.[16] used PBPK modeling to study the influence of transporter ontogeny on the relative contribution of glomerular filtration and active tubular secretion to renal clearance (CL_R) for drugs with different properties in pediatric subjects (1 day to 15 years). They studied a set of 3800 hypothetical drugs generated by varying the following compound properties: protein binding, blood:plasma and tissue partition ratios, and transporter-mediated intrinsic clearances (via retrograde calculation of adult values). Independent of pediatric age, if the relative ontogeny of renal transporters were less than 0.2 of adult values, the predictions were deemed unacceptable. Similarly, for children younger than 2 years of age, ignoring transporter ontogenies resulted in CL_R predictions that were unacceptable. This study illustrates the realized potential that P-PBPK modeling provides in defining at what stage of pediatric development transporter ontogeny cannot be ignored.

Biologics

Basu et al.[17] investigated the utility of a generic PBPK model scaled down to children to predict the observed concentration-time courses of two humanized immunoglobin G1 (IgG1) monocolonal antibodies, palivizumab (directed against the F-protein of respiratory syncytial virus), and bevacizumab (that binds to vascular endothelial growth factor) in pediatric subjects. Palivizumab P-PBPK model predictions, when compared with observed data in infants with either bronchopulmonary dysplasia or who were born prematurely, revealed area under the curve (AUC) predicted/observed ratios that were between 0.75 to 1.56 across the dosing range (3–15 mg/kg). Conversely, bevacizumab simulations assuming a median age of 13 years (similar to the observed data) underpredicted clearance and reported predicted/observed ratios for AUC were within the interval of 1.32 to 1.54. This study highlights the need to close knowledge gaps via further experimental data.

Formulation

The utility of P-PBPK in differentiating between extrinsic (e.g., drug, food, and formulation) and intrinsic (e.g., gastrointestinal developmental anatomy and physiology) variables affecting oral absorption has been shown for sotalol and paracetamol.[18] The authors constructed and validated adult PBPK models of both compounds before extrapolating to pediatric populations. Despite this,

the underprediction of maximal concentration (C_{max}) and overprediction of time to maximal concentration was made for both compounds in children younger than 2 years of age. Sensitivity analysis revealed that mean gastric emptying time was slowed in infant and neonate groups that may have been related to osmolality, viscosity, and calorific density of the food.

Clinical

Pharmacokinetics

Tacrolimus is used in organ transplant patients to prevent organ rejection. Emoto et al.[19] developed adult and pediatric renal transplant PBPK models to evaluate the variability of tacrolimus PK in these populations. Adult CYP3A5 elimination was optimized via sensitivity analysis of the observed mean ratio of minimum measured concentration of drug prior to next dose (C_{trough}) between poor (*CYP3A5*3*) and normal (*CYP3A5*1*) metabolizers. Subsequently, virtual pediatric patients were generated by incorporating changes in hematocrit (30% lower than default), hepatic CYP3A4 ontogeny (both Upreti and Wahlstrom[20] and Salem et al.[21]), and the aforementioned changes to CYP3A5 observed in transplant patients. Simulations of pediatric patients with twice daily tacrolimus dosing (0.05–0.2 mg/kg) for 3 weeks yielded predictions that were similar to the POP-PK model, and a colinear trend was observed between age and bodyweight. Thus, incorporating pathophysiological changes in elimination pathways and biochemical parameters exemplifies the utility of P-PBPK in the prospective identification of covariates ahead of any intended clinical investigation.

Dose selection

Ethical considerations are of primary importance when considering clinical investigations in neonates. Neonatal cohorts are rapidly developing anatomically and physiologically and therefore an especially vulnerable group. Gentamicin is a narrow therapeutic aminoglycoside antibiotic, and its therapeutic efficacy is associated with peak (C_{max}) plasma concentrations and safety with C_{trough} <1 μg/ml.[22] The authors verified a PBPK-PD model of gentamicin in adults and preterm neonates. Dosing regimens where C_{trough} was maintained either above or below 1 μg/ml were identified from clinical data obtained from a neonatal intensive care unit. Model predictions indicated that dosing regimens of 5 mg/kg of gentamicin every 36 h, rather than the standard regimen of 4 mg/kg every 24 h, was preferable in attaining higher C_{max} and lower C_{trough} concentrations. This example illustrates the utility of P-PBPK modeling in maximizing therapeutic efficacy and safety while decreasing the probability of bacterial resistance from exposure to the antibiotic.

Formulation

Antiepileptic drugs are frequently prescribed in children not only to treat seizures related to epilepsy but also other neurological conditions. An adult PBPK model was constructed and qualified to evaluate the DDI potential of lamotrigine in both immediate (IR) and extended (XR) release formulations. Similarly, a pediatric PBPK model was constructed and qualified against single-dose and multiple-dose clinical data obtained from the literature for the immediate formulation in children 4–17 years of age.[23] Single-dose immediate formulation (2 mg/kg) simulations reflected the observed data well, predicted/observed ratios of C_{max} and AUC were 1.15 and 0.92, respectively. Once-daily multiple-dose studies of either 7.7 or 9.4 mg/kg yielded predicted/observed ratios in the minimum plasma concentration (C_{min}) of 1.05 and 0.86, respectively. The utility of P-PBPK modeling is apparent in quantitatively assessing differences between formulation dispositions in adults and children.

CONCLUSION/DISCUSSION

The historical growth in the number of publications involving P-PBPK modeling reflects the general growth in the use of these models.[4] According to El-Khateeb et al.,[4] there were approximately 102 PBPK studies published in 2019 in all areas of applications. Based on our data, P-PBPK made up around 31% (32/102) of such publications for that year in contrast to 2009 where it was approximately 4%. The growth in the use of P-PBPK modeling is not surprising given its recognized potential, for instance, to replace clinical studies,[24] support clinical questions,[25] and inform dose projection in neonates, infants, and children.[26] The latter application is increasingly being used by the pharmaceutical industry as a more mechanistic means of dose extrapolation for pediatric clinical trials defined in a PIP or PSP.

The growth of P-PBPK modeling has, in part, been facilitated by the development of commercial user-friendly platforms featuring graphical user interfaces; of the studies we identified, 86% used a commercial platform. Of the drug development applications, all of them used commercial packages that offer more comprehensive verification of the models as demanded by regulators.[27] Although commercial software was also dominant for the clinical and model development application, there was more use of general modeling tools such as MATLAB. This is probably because of the fact that the user has more control over the model code. A more comprehensive discussion

of the relative merits of commercial software is given by El-Khateeb et al.[4]

Although it is recognized that there are an increasing number of applications of P-PBPK in drug development, POP-PK remains the mainstay of modeling approaches supporting MIDD.[12] Among 105 new pediatric indications approved by the FDA between January 2017 and June 2019, it was reported that MIDD was applied in 64 cases (61%), with POP-PK modeling being used in all of them.[12] Although the relative merits of PBPK modeling as applied to pediatric scenarios were discussed, statistics relating to the use of PBPK modeling were not cited. Thus, it appears that the role of P-PBPK modeling in pediatric drug development has yet to be fully established and indeed acknowledged. This is likely to change during the next few years as the number of metabolically stable compounds, which are more susceptible to transporter-mediated efflux and complex absorption issues, continue to increase in drug discovery and development portfolios. Mechanistic models, such as PBPK, are required to describe the distribution and disposition of these compounds, including enzyme-transporter interplay. Extrapolation in pediatric subjects will require the age-related physiological changes relevant to each of these mechanistic processes that are already accommodated in P-PBPK models.[9]

The findings of our study confirm that there has been a significant increase in the P-PBPK publication rate from academia, the pharmaceutical industry, and regulators, reflecting the broad utility of this modeling approach. In terms of primary classification, clinical application remains the main category, indicating the widespread use of P-PBPK by academic groups involved in pediatric clinical pharmacology. However, it should be noted that there has been a rapid rise in the use of P-PBPK models in drug development, which is likely to increase during the coming years. This to some extent will be dependent on further development and verification of the pediatric models and their acceptance by the regulators. It is envisaged that the ever-increasing number of publications relating to verification will provide additional support in gaining acceptance of PBPK modeling in areas beyond just dose extrapolation[26] and increase the level of confidence in this approach.

The secondary applications in each primary group were generally as expected. Dose selection is the most common pediatric drug development application followed by formulation (e.g., formulation bridging). Interestingly, few biologics examples were seen in this category, but this is an area of growing interest and is illustrated by additional biologics studies featured in the model development and evaluation category. Because allometric scaling does not always provide the correct dose, more mechanistic biologic P-PBPK models that account for the ontogeny of factors such as the neonatal Fc receptor (FcRn) and endogenous and exogenous immunoglobulin G are desirable.[28] The expectation is that this will continue to be an area of research focus both in terms of model development (unknown age-related changes) and application.

DDI prediction is the most frequent application of adult PBPK modeling, and there are many case studies indicating acceptance of PBPK modeling by regulators in lieu of actual clinical studies.[8] Accurate DDI predictions in adults requires an assignment of clearance routes and metabolic pathways based on robust data. In pediatric subjects, successful DDI predictions are largely dependent on accurate ontogeny information relating to the individual clearance mechanisms.[29] The DDI liability of a drug may change in children of different ages as a result of the relative ontogenies. Indeed, this is one of the perceived strengths of P-PBPK models and has been recently investigated as part of a regulatory submission.[30] The study of pediatric DDIs is necessary to develop safe medicines; as well as the further evaluation of P-PBPK models, there is a need to generate clinical pediatric DDI data for verification purposes.[25,31]

Few P-PBPK models were found that linked in PD, and less is known about pediatric developmental PD.[32] Thus, this should be a focus for future research as linking in effect models can improve dose prediction, especially in neonates.[7] Likewise, pediatric toxicology is an area where there are few applications. PBPK has historically been used by toxicology groups to model exposures of environmental chemicals[1] and could be applied to assess tissue exposures and related toxicity of drugs in children (e.g., the hepatotoxicity seen in greater frequency in children for sodium valproate).[33] Trial design is another area where PBPK modeling is underused. There are good examples of how P-PBPK modeling has been used in optimal pediatric trial design.[34] P-PBPK models can be used to generate age-related PK data that are then analyzed using POP-PK software. In turn, the results are fed into a D-optimal design package based on the Fisher information matrix to determine optimal PK sampling timepoints for a clinical study.

Limitations in the current analysis are that no independent assessment was made regarding the quality of individual research publications, although all were from known peer-reviewed journals. The classification was not always clear cut, for example, a biologics article that also assesses dose and a DDI article that is also referring to the prediction of dose. Categorization was generally assessed by focusing on the main theme of the research. In some of the categories, such as clinical, it may be worthwhile undertaking further analysis to assess the number of applications related to areas such as personalized medicine in pediatrics. Despite our interest, we felt that this topic was beyond the scope of the research described here.

In conclusion, P-PBPK models are being increasingly used as part of MIDD, and the case studies presented illustrate that integrating and leveraging existing knowledge[35] allows a more mechanistic approach to inform dose selection (e.g., small and large molecules) and formulation bridging and extrapolate DDIs. Despite the recognized potential of P-PBPK modeling, the approach still appears to lag behind other approaches, such as POP-PK in pediatric drug development. To this end, collaborative efforts[8] by model providers and academic, industry, and regulatory authorities are required to continue to advocate the use of P-PBPK models in drug development and clinical settings. Furthermore, increased application and research in this area can help to identify and "plug" knowledge gaps associated with pediatric system parameters as well as provide additional verification of the population model to gain more confidence and acceptance of the approach.

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CONFLICT OF INTEREST

All of the authors are employees of Certara UK Limited and may hold shares in Certara. As an Associate Editor of *CPT: Pharmacometrics & Systems Pharmacology*, Karen Rowland Yeo was not involved in the review or decision process for this article.

AUTHOR CONTRIBUTIONS

T.N.J., B.G.S., and K.R.Y. wrote the manuscript. T.N.J. and K.R.Y. designed the research. T.N.J. and B.G.S. performed the research. T.N.J., K.R.Y., and B.G.S. analyzed the data.

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SUPPORTING INFORMATION

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