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Predictive Performance of Physiology-Based Pharmacokinetic Dose Estimates for Pediatric Trials: Evaluation With 10 Bayer Small-Molecule Compounds in Children

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Abstract

Development and guidance of dosing schemes in children have been supported by physiology-based pharmacokinetic (PBPK) modeling for many years. PBPK models are built on a generic basis, where compound- and system-specific parameters are separated and can be exchanged, allowing the translation of these models from adults to children by accounting for physiological differences. Owing to these features, PBPK modeling is a valuable approach to support clinical decision making for dosing in children. In this analysis, we evaluate pediatric PBPK models for 10 small-molecule compounds that were applied to support clinical decision processes at Bayer for their predictive power in different age groups. Ratios of PBPK-predicted to observed PK parameters for the evaluated drugs in different pediatric age groups were estimated. Predictive performance was analyzed on the basis of a 2-fold error range and the bioequivalence range (ie, $0.8 \leq$ predicted/observed ≤ 1.25). For all 10 compounds, all predicted-to-observed PK ratios were within a 2-fold error range ($n = 27$), with two-thirds of the ratios within the bioequivalence range ($n = 18$). The findings demonstrate that the pharmacokinetics of these compounds was successfully and adequately predicted in different pediatric age groups. This illustrates the applicability of PBPK for guiding dosing schemes in the pediatric population.

Keywords

clinical trials (CTR), dose prediction, PBPK, pediatrics (PED), physiology (PHY)

During the past 15 years, physiology-based pharmacokinetic (PBPK) modeling has been the scientific foundation to match the exposure in a pediatric population to the target exposure, that is, a known reference exposure clinically observed in an adult patient population at a safe and efficacious dose. PBPK models are mechanistic models that separate compound-specific properties (such as lipophilicity and molecular weight) from system-specific parameters (such as organ volumes and blood flows). Therefore, PBPK models are built on a generic basis and can be reparameterized, allowing the translation to a population with a different physiology. Because of these features, PBPK modeling is an increasingly popular approach to support decision making for dosing in relevant subpopulations of special clinical interest, such as children. This is also supported by regulatory authorities.[1,2]

PBPK models incorporate age-dependent changes of relevant anthropometric and physiological parameters and apply ontogeny and variability of active processes involved in the absorption, distribution, metabolism, and elimination of pharmaceutical compounds.[3,4] As most of these changes occur in the first 2 years of life, such as maturation of the liver and kidney function, in contrast to other changes that occur later in a child's life, for example, during puberty, a good understanding of this age dependency is of utmost importance. An overview of relevant processes and properties that are known, less known, or need further elucidation has been previously described.[5]

Already in the early phase of drug development in adults, dosing in children is discussed. In the absence of clinical data in children, a PBPK model is first built based on physicochemical information and concentration-time data from adult pharmacokinetic (PK) studies. As a next step, the translation of the adult

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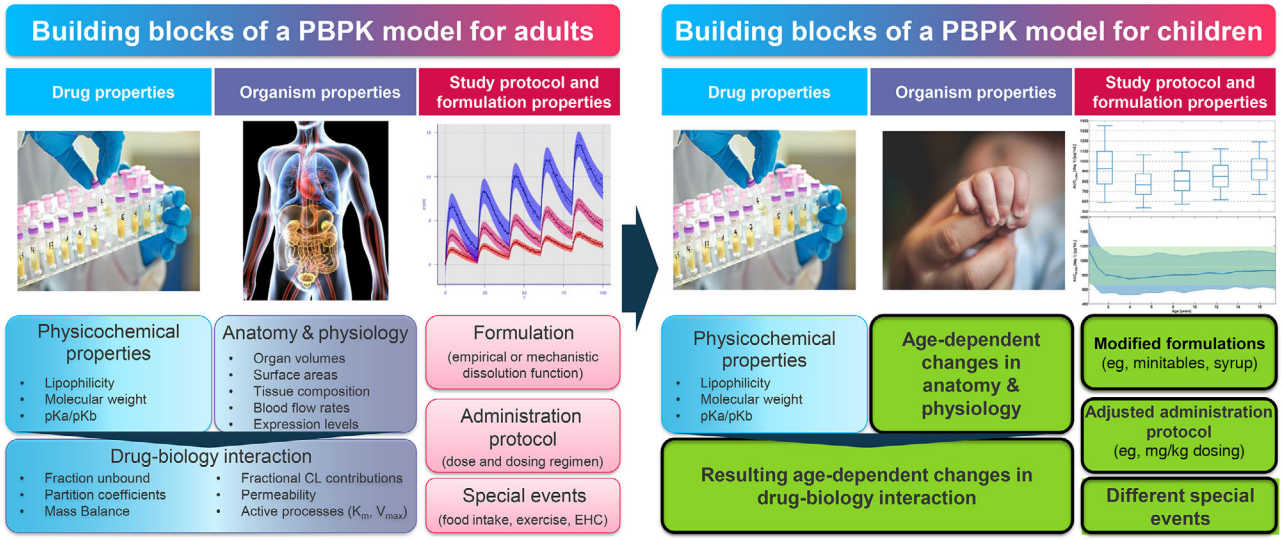

Figure 1. Building blocks of a PBPK model for adults and the parameters adjusted when translating to a PBPK model for the pediatric population. PBPK, physiology-based pharmacokinetic. (Adapted from Kuepfer et al, Figure 2.[7])

PBPK model to children—initially purely predictive—is made on the basis of the existing knowledge on age-related anthropometry, physiology, and active processes, such as enzyme and transporter activities.[5,6] Subsequently, when clinical data become available during the pediatric development program, PBPK-based predictions transition into a descriptive mode as the PBPK model may be refined and is used to integrate and interpret the observed clinical data.

To date, PBPK predictions from several studies informed dosing decisions and streamlined the clinical study design for 10 Bayer small-molecule compounds. In this analysis, we evaluate the predictive performance of pediatric PBPK models for these compounds in different age groups. These models were applied to support clinical decision processes, such as identifying dose levels and dosing intervals, sampling schemes, and cohort sizes.

Methods

The workflow for constructing and translating a PBPK model from adults to children is well described.[6–11] An overview of relevant building blocks to construct a PBPK model for adults and the parameters adjusted during translation to children for use in pediatric clinical development is exemplarily illustrated in Figure 1. The building blocks of a PBPK model are categorized into drug- and system-specific properties, study protocol, and formulation characteristics. Some parameters are dependent on a combination of both drug- and physiology-specific parameters (drug-biology interaction), such as fraction unbound or membrane permeability. For the parameterization of the adult and pediatric PBPK models and for the simulation of PK parameters of 10 small-molecule Bayer compounds, the existing model for each compound was applied for this analysis (Table 1). The PBPK models for amikacin, gadovist, and magnevist were updated to PK-Sim version 9,[20,21] as additional simulations needed to be performed for this analysis, which is described in more detail below. As the developed PBPK models that were applied for clinical decision making have been filed for regulatory request, most of these models are also already published, whereas some of them are still part of the ongoing drug development program.[3,12–17]

To evaluate the predictive performance of the PBPK models, we calculated the ratio of PK parameters predicted by PBPK before study conduct vs PK parameters estimated by population pharmacokinetics (PopPK) and noncompartmental analysis (NCA) post hocs after clinical pediatric study data became available. For clinical studies in children, especially when small children are included, the collected data are typically very sparse, and PopPK assessment was preferred over NCA for comparison. However, PopPK-derived PK parameters were not always available (eg, for amikacin, riociguat). The aggregation of PK parameters derived from PBPK and PopPK simulations is outlined below for each compound. Integral exposure measures, clearance, or concentrations at specific times after dosing were explored depending on the availability of pediatric study data per compound. The PK parameters for each compound were selected on the basis of the relevant primary PK parameter applied for the respective analyses for calculating pediatric doses.

The ratio of the PK parameters for each compound was calculated and categorized into the predefined age

Table 1. An Overview of 10 Small-Molecule Bayer Compounds Applied in Children Since 2005, the Age Ranges of Children With Available Clinical Data, and the Clearance Processes Included in the PBPK Model

Compound Name	Age Range, y	Source Published Clinical Data	Involved Processes in PBPK Model	Route of Administration In Children
Amikacin	0.01-16	[27,28]	GFR	IV
Ciprofloxacin	0.2-6.6	[36,37]	CYP1A2, TS, GFR, Bil.CL	PO
Copanlisib	13-17	…	CYP3A4, P-gp, BP	IV
Gadovist	0.2-18	[38,39]	GFR	IV
Levonorgestrel	12-18	…	Hepatic clearance	IU
Magnevist	0.2-2	…	GFR	IV
Moxifloxacin	0-18	[44,45]	UGT1A1, SULT2A1, Bil.CL, GFR	PO
Regorafenib	2-17	[47]	CYP3A4, UGT1A9, Bil.CL	PO
Riociguat	6-18	…	CYP1A1, CYP3A4, CYP3A5, CYP2C8, CYP2J2,UGT1A2, UGT1A9, Bil.CL (P-gp, BCRP), TS/GFR	PO
Rivaroxaban	0.5-18	[52]	CYP3A4, Plasma Hydrolysis, GFR, TS, CYP2J2	PO

BCRP, breast cancer resistance protein; Bil.CL, biliary clearance; BP, hypothetical binding partner; CYP, cytochrome P450; GFR, glomerular filtration rate; IU, intrauterine; IV, intravenous; P-gp, P-glycoprotein; PO, per os; SULT, sulfotransferase; TS, tubular secretion; UGT, uridine 5'-diphospho-glucuronosyltransferase.

groups: neonates and infants from 0 to <2 years of age, preschool children from 2 to <6 years of age, school children from 6 to <12 years of age, and adolescents from 12 to <18 years of age.[18,19]

Data

An overview of Bayer small-molecule compounds applied in this analysis is shown in Table 1. This table also illustrates the available clinical data for the compounds, including the age ranges of children that were used in this analysis. Compounds were considered for this retrospective analysis in case clinical data has already been obtained in pediatric age groups.

Software

All PBPK models were built using the Open Systems Pharmacology (OSP) software, formerly known as commercial software tools PK-Sim and MoBi, which is now freely available as OSP Suite under the GPLv2 License, where source code and content are public. For the calculation and illustration of the PK ratios, Rstudio (R version 3.6.2; R Foundation for Statistical Computing, Vienna, Austria) was used.

Building and Evaluating the Adult PBPK Models

For amikacin,[3] ciprofloxacin,[15] copanlisib,[14] levonorgestrel,[12] moxifloxacin,[17] regorafenib,[13] and rivaroxaban,[16] building and evaluation of the PBPK models have been presented or published previously. The other PBPK models have been used to inform clinical trials. For all compounds that are used in this analysis, an adult PBPK model was created initially and evaluated, as described more recently in the workflow by Maharaj et al[9] and illustrated previously.[5]

Translation of Adult PBPK to Children

Pediatric PBPK models were established using the developed and verified (adult) PBPK model for each compound by translating the adult physiology, clearance process(es), protein binding, and the process-specific variabilities to children (Figure 1). A pediatric translation workflow for constructing a PBPK model in pediatric clinical development has been also illustrated previously.[5] No fitting of the pediatric model parameters was performed. During the translation of adult PBPK models to children, the following assumptions (if unknown) and considerations were made:

- When translating the adult model to children, it is assumed that the contributing metabolism and excretion pathways are qualitatively the same in children as in adults.
- No further changes to model parameters describing drug or drug-biology interacting properties (eg, lipophilicity, intestinal permeability, solubility) are allowed in the PBPK models for children.
- There is identical pathophysiology in children as in adults.

The predictions of the PK parameters in the pediatric subgroups by the PBPK model and the PopPK or NCA of clinical data-based calculations were summarized for each compound as geometric means and used to evaluate predictive performance. Ratios of predicted to observed PK parameters for the evaluated drugs in different pediatric age groups were then investigated for being within a 2-fold error range and within the bioequivalence range (ie, $0.8 \leq$ predicted/observed ≤ 1.25). Although a bioequivalence range assessment is meant to demonstrate 2 different formulations to be "equivalent" at a certain dose level, in this analysis it

was applied for PK exposure matching. Therefore, a match-failure would not mean that the whole pediatric dosing approach failed.

Anthropometric and Physiological Information

PK-Sim incorporates literature-based age dependencies of anthropometric (eg, height, weight) and physiological (eg, blood flows, organ volumes) parameters, which were generally used as default values for the simulations in children.[3,4]

The applied ontogeny and variability of active processes and plasma proteins that are built-in into PK-Sim for translation to children are described in the publicly available PK-Sim Ontogeny Database Version 7.3,[22] or otherwise referenced for the specific process for each compound.

For each compound, the estimates of the predicted PK parameters in the pediatric subgroups were derived from PBPK modeling. PopPK or NCA models of clinical data were aggregated as geometric means and used for ratio calculation.

Drug Examples

Building and evaluation of the adult PBPK models, and the translation to children for 10 small-molecule Bayer compounds was performed as described in the Methods section. Below, a summary of key parameters of the adult PBPK models relevant for development of the pediatric models, and the evaluation of the pediatric models are described.

Amikacin. Amikacin is an aminoglycoside antibiotic used for the treatment of a number of serious infections.[23]

Adult Model Development. Amikacin is excreted primarily by glomerular filtration.[24,25] The PBPK model for amikacin was previously built for adults and preterm neonates.[3,26] As the latter model was built more recently, this PBPK model was evaluated in adults first before predicting the PK in the different pediatric age groups without further changes. Only amikacin PK data after intravenous administration were applied for this analysis, using PK-Sim version 9.1. The available clinical PK data were derived from different literature sources and were here used for PBPK prediction and verification purposes.

Pediatric Model Evaluation. The clearance of amikacin in children was predicted purely based on knowledge about kidney maturation[3] and, accordingly, developmental changes in glomerular filtration rate (GFR). For evaluating the predictive performance in children, all available reported PK data in children were used. Individual simulations were performed on the basis of the demographics of each child. The predicted clearances were aggregated as geometric means for each predefined age group as described for their comparison with the aggregated reported clearances from literature.[27,28] As the clinical study data for amikacin were based on literature data only, the individual PK ratios were additionally calculated and plotted (Figure 2).

Ciprofloxacin. Ciprofloxacin belongs to the quinolone antibiotics class, that is used to treat a wide variety of bacterial infections.

Adult Model Development. A ciprofloxacin PBPK model was built and evaluated for the predictive performance toward pediatric and geriatric patients, using PK-Sim and MoBi version 7.2.0.[15] Both intravenous and orally administered ciprofloxacin PK data were available for analysis. To reflect the known elimination pathways of ciprofloxacin,[17] the PBPK model included renal clearance and hepatic clearance. The renal clearance processes were glomerular filtration and an unspecific tubular secretion (TS) accounting for the exceeding renal clearance.[29,30] The hepatic clearance processes were cytochrome P450 (CYP) 1A2-mediated elimination[31] and an unspecific biliary secretion to account for a suggested rapid gastrointestinal transcellular secretion of ciprofloxacin.[32–35] Based on oral PK data in adults, the net active drug uptake and dissolution profiles were estimated, by means of estimating a multiplier for the intestinal permeability of each gastrointestinal tract segment. The formulation and granulate disintegration and dissolution of the oral dose forms were described by a Weibull function. The available reported clinical PK data were derived from different former studies and used to evaluate the PBPK prediction for verification purposes.

Pediatric Translation. For evaluating the predictive performance in children, the available reported mean exposures (area under the concentration-time curve [AUC] from time 0 to infinity) in each pediatric age group, mean individual PBPK predictions were made on the basis of the mean demographics of the children.[36,37] The estimated exposures were aggregated as geometric means for each predefined age group for their comparison with the aggregated means of the reported exposures.

Copanlisib. Copanlisib is a phosphatidylinositol 3-kinase inhibitor that is approved by the US Food and Drug Administration for the treatment of adult patients experiencing relapsed follicular lymphoma who have received at least 2 prior systemic therapies.[14]

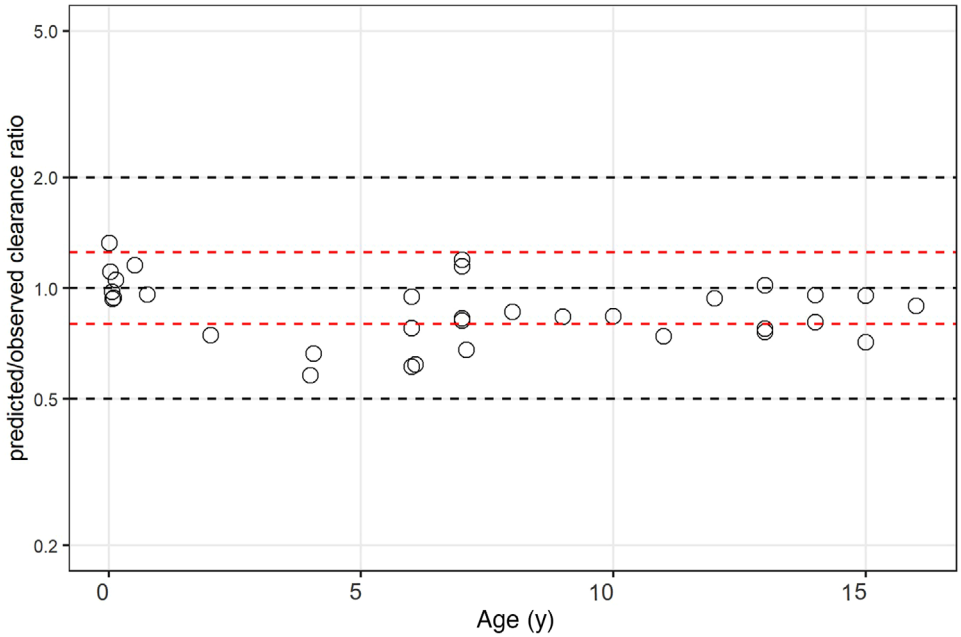

Figure 2. Individual ratios of predicted to observed clearance for amikacin at different ages. The open circles represent the individual clearance ratios. Black dotted lines indicate 0.5, 1- and 2-fold prediction intervals. Red dotted lines indicate 0.8- and 1.25-fold prediction intervals.

Adult Model Development. A PBPK model for copanlisib in adults was created and evaluated using PK-Sim version 8.0.[14] The copanlisib PBPK model includes a hepatic clearance process mediated by CYP3A4, a P-glycoprotein–mediated drug transport, and a hypothetical tissue-binding partner.

Pediatric Translation. The adult PBPK model was translated to children to support clinical decision making of copanlisib application in pediatric patients. Available individual PK data in adolescents were used to calculate an aggregated geometric mean exposure (area under the concentration-time curve from time 0 to 168 hours after the last dose). The PBPK predictions for each individual matched to the adolescent's demographics were aggregated by calculating the geometric mean of the individual AUC from time 0 to 168 hours after the last dose for the adolescent age group.

Gadovist and Magnevist. Gadovist and magnevist are gadolinium-based extracellular contrast agents and have been proven to be effective contrast media in adults and children for contrast-enhanced magnetic resonance imaging.

Adult Model Development. Gadovist and magnevist are both excreted primarily by glomerular filtration.[38–40] Therefore, the clearance of both contrast agents was predicted solely on the basis of knowledge about kidney maturation and developmental changes in GFR built in PK-Sim. The PBPK models for gadovist and magnevist that have been applied to support clinical decision making were updated to PK-Sim version 9.0 before simulating the PK for each predefined pediatric age group.

Pediatric Translation. Compared to the original PK-Sim models (version 4) that were used elsewhere, in PK-Sim version 9.0, the method of Hayton,[41] as modified by Edginton et al,[42] is built in to scale glomerular filtration to children. Thereafter, the aggregated geometric mean clearance for each age group was calculated and compared to the available reported (aggregated) clearances for gadovist[38,39] and magnevist after intravenous administration.

Levonorgestrel. Levonorgestrel is a progestin hormone used in a variety of contraceptive products.[43]

Adult Model Development. A PBPK model was built in PK-Sim version 4.1 for the levonorgestrel contraceptive system intrauterine device in female adults using observed data from clinical studies after intravenous or oral administration of levonorgestrel.[12] An unspecific clearance to account for metabolism was used. The PBPK model included all relevant physiological properties of the uterus and the administration of levonorgestrel by an intrauterine device.

Pediatric Translation. The adult PBPK model was translated to adolescent girls and respective PK parameters for the adolescent postmenarche population were

predicted.[12] The aggregated levonorgestrel concentrations after 365 days (geometric mean) were compared to the observed aggregated concentrations (geometric mean values) of the clinical study data.

Moxifloxacin. Moxifloxacin is fluoroquinolone and is applied for the treatment of bacterial infections, such as complicated intra-abdominal infections.

Adult Model Development. A PBPK model for moxifloxacin was built using PK-Sim version 4.2 and MoBi version 2.3 after both oral and intravenous administration of moxifloxacin. The PBPK model includes a renal clearance process mediated by glomerular filtration and 2 hepatic processes, mediated by sulfate conjugation via sulfotransferase 2A1 and glucuronidation via uridine 5'-diphospho-glucuronosyltransferase (UGT) 1A1.[17] An unspecific biliary secretion was included to account for the gastrointestinal transcellular secretion of moxifloxacin and its metabolites.[17] The specific clearance via sulfotransferase 2A1, UGT1A1, and biliary excretion was assumed to be independent of age (ie, the same activity per gram tissue weight as in adults).

Pediatric Translation. The method of Hayton,[41] as modified by Edginton et al,[42] was used to scale the adult GFR to children. For evaluating the predictive performance in children, the PopPK-based results were applied as representative of the observed data, by aggregation of the calculated geometric mean of the individual PopPK clearance estimates[17] from the individual patients for each age group.[44,45] The PBPK predictions for each individual matched to the individual's demographics were aggregated by calculating the geometric mean of the individual clearances for each predefined age group.

Regorafenib. Regorafenib is an approved oral multikinase inhibitor for the treatment of patients with advanced cancer (colorectal carcinoma, gastrointestinal stromal tumors, and advanced hepatocellular carcinoma).[46]

Adult Model Development. A PBPK model for regorafenib and its active metabolites was built using PK-Sim version 4.2.5 to support dose selection for the pediatric dose-finding study and to estimate exposure based on sparse PK sampling.[13] The PBPK model includes the different processes representing phase I (CYP3A4) and phase II metabolism (UGT1A9) for the parent drug and metabolites implemented in the liver, kidney, and gut lumen. The transport processes for one of the metabolites mediated by P-glycoprotein are covered by clearance processes as well. The model includes estimated individual dissolution profiles to capture the observed high variability in the absorption of regorafenib in adults, considered to be caused by variability in luminal dissolution resulting from interindividual variability in intestinal liquid volumes and bile salt concentrations.

Pediatric Translation. For evaluating the predictive performance in children, the PopPK model–based results were applied, by aggregation of the calculated geometric mean of the individual simulated exposure (AUC from time 0 to 24 hours after the last dose in steady state [$AUC_{24,ss}$]) estimates[13] from the individual patients for each age group.[47] The PBPK predictions for each individual matched to the demographics of the individual patients were aggregated by calculating the geometric mean of the individual $AUC_{24,ss}$ for each predefined age group.

Riociguat. Riociguat is a direct stimulator of the soluble guanylate cyclase and is used to treat 2 forms of pulmonary hypertension: pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension in adults.[48]

Adult Model Development. Among other indications, riociguat is under investigation for treatment of PAH in children.[49] A PBPK model for riociguat in adults was built using PK-Sim version 4.2 to predict the PK of riociguat in children of various age groups suffering from PAH following oral administration of multiple doses. The riociguat PBPK model includes renal clearance processes mediated by glomerular filtration and TS. Metabolism of riociguat occurred via oxidative biotransformation by CYP2C8, 2J2, 3A4/3A5, and CYP1A1 into its major metabolite, and to account for the gastrointestinal transcellular secretion unspecific biliary secretion were included.[50]

Pediatric Translation. For evaluating the predictive performance in children, available individual through plasma concentrations at steady-state ($C_{trough,ss}$) in adolescents were aggregated into geometric mean $C_{trough,ss}$ for each cohort. The PBPK predictions for each individual matched to the individual's demographics were aggregated by calculating the geometric mean of the individual $C_{trough,ss}$ for the adolescent age group.

Rivaroxaban. Rivaroxaban, an oral anticoagulant (a direct factor Xa inhibitor) used to treat and prevent blood clots, has been approved in adult patients for several thromboembolic disorders.[16,51]

Adult Model Development. A PBPK model for rivaroxaban was developed using PK-Sim version 4.2 and MoBi version 2.3 and evaluated in adults and children to inform the dosing regimen of rivaroxaban in pediatric patients.[16,52] The PBPK model already included a model for gastrointestinal transit and absorption,

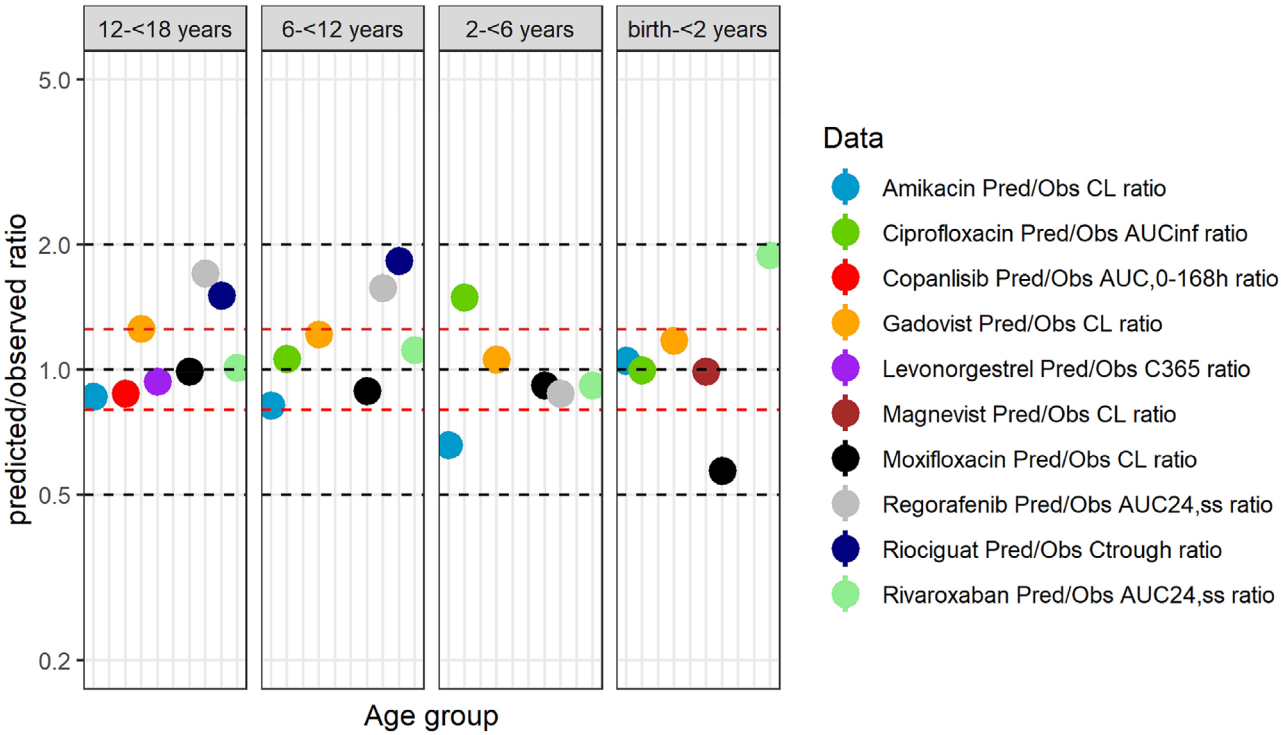

Figure 3. Ratios of predicted to observed PK parameters for the evaluated drugs in different pediatric age groups. The age groups are sorted in descending order from adolescents (left) to neonates and infants (right). The different colors represent the different compound PK ratios. The different symbols represent the different PK parameters. Black dotted lines indicate 0.5, 1-, and 2-fold prediction intervals. Red dotted lines indicate 0.8- and 1.25-fold prediction intervals. $AUC_{0\text{-}168h}$, area under the concentration-time curve from time 0 to 168 hours; $AUC_{24,ss}$, area under the concentration-time curve from time 0 to 24 hours after the last dose in steady state; AUC_{inf}, area under the concentration-time curve from time 0 to infinity; C_{365}, levonorgestrel concentration after 365 days; CL, clearance; C_{trough}, trough concentration.

which is part of PK-Sim version 5.0 and higher.[53,54] The rivaroxaban PBPK model includes 2 renal clearance processes mediated by glomerular filtration and an unspecific TS accounting for the exceeding renal clearance, and 3 hepatic clearance processes, 2 of which are mediated by CYP3A4, CYP2J2, and another CYP-independent hydrolysis of rivaroxaban.[55–57]

Pediatric Translation. PBPK predictions for children from term neonates (≥2 kg) to adolescents aged 18 years were aggregated by calculating the geometric mean of the individual exposure ($AUC_{24,ss}$) for each predefined age group and compared to the aggregated geometric mean of the PopPK-based individual $AUC_{24,ss}$ estimates for each age group, that were used as representative of the observed data.[52]

Results

The available clinical study data and their reported PopPK or NCA of clinical data-based calculations of the compounds were collected for available age groups (Table 1).

For the individual clearances of amikacin, resulting overall predictivity of the PBPK model in children is exemplarily shown in Figure 2. All individual clearance ratios (n = 33) fell within a 2-fold error range, with 64% (n = 21) within the bioequivalence range (Figure 2). The overall geometric mean fold error was calculated to be 1.22.

The aggregated mean ratios for each compound were successfully predicted for all age groups where observed data were available (neonates and infants, preschool children, school children, and adolescents). Figure 3 shows the mean PK parameter ratios of the investigated compounds predicted in different pediatric age groups. Figures 4 and 5 additionally illustrate the results separately for drugs where either the primary or secondary PK parameters were used for their evaluation in different pediatric age groups. For all compounds, the 27 calculated PK ratios in all pediatric age groups were predicted within a 2-fold error range, with 67% (n = 18) of the predicted ratios being within the bioequivalence range. The highest overestimation and underestimation of an observed PK parameter was observed in the youngest age group (for rivaroxaban and moxifloxacin, respectively).

Comparing PK ratios of only passively eliminated compounds (9 ratios for 3 compounds) with actively eliminated compounds (18 for 7 compounds), as shown

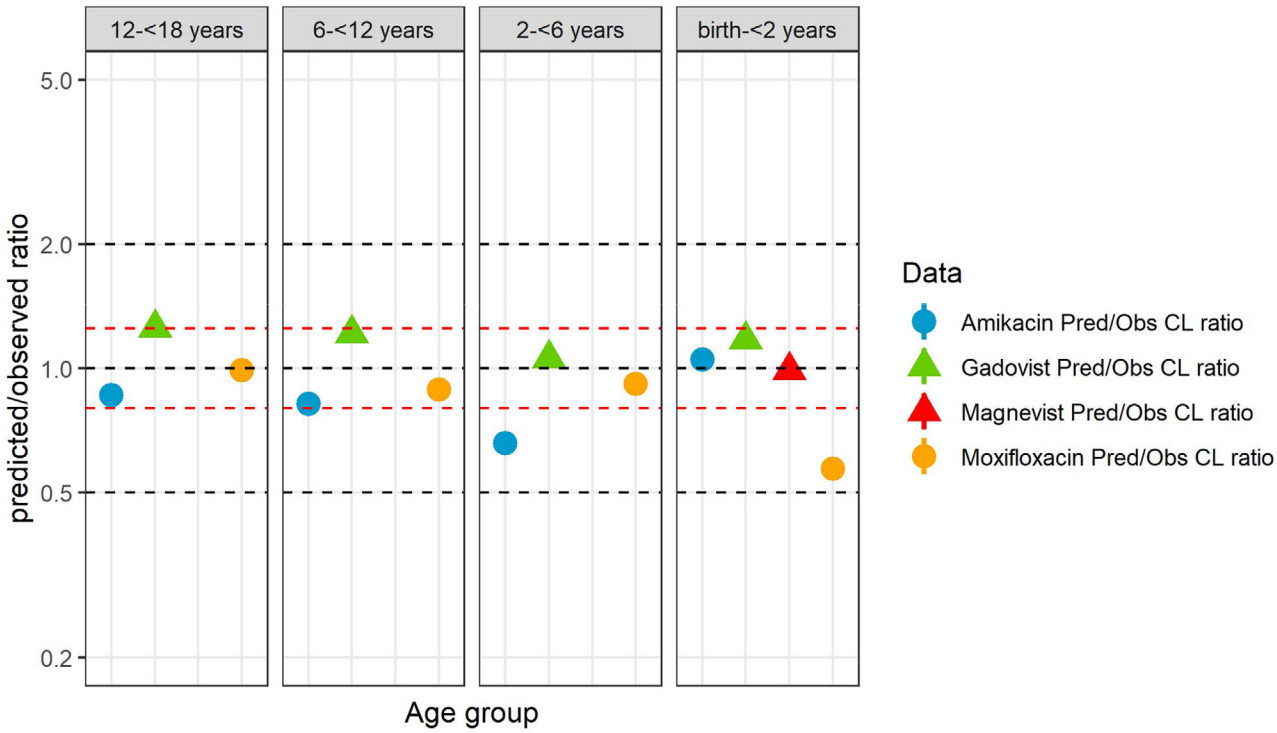

Figure 4. Ratios of predicted to observed primary PK parameters for the evaluated drugs in different pediatric age groups. The age groups are sorted in descending order from adolescents (left) to neonates and infants (right). The different colors represent the different compound PK ratios. The different symbols represent the different PK parameters. Black dotted lines indicate 0.5, 1-, and 2-fold prediction intervals. Red dotted lines indicate 0.8- and 1.25-fold prediction intervals. CL, clearance.

in Figure 6, it was evident that the prediction was slightly better for passively eliminated compounds compared to actively eliminated compounds, with 78% being within the bioequivalence range vs 61%, respectively.

Discussion

PBPK predictions for small-molecule drugs in children are well established in drug development, in particular to support and streamline clinical decisions during drug development in children (eg, specification of dosing regimens, sampling schemes, cohort size). This is also reflected by the constantly high number of this application scenario in submissions to the US Food and Drug Administration.[1] The aim of this methodological study was to further evaluate the application of pediatric PBPK models in drug development. To this end, this study evaluated the predictive performance of pediatric PBPK models for 10 small-molecule compounds developed by Bayer with clinical data in pediatrics. An evaluation metric, the ratio of predicted to observed PK parameters estimated in different pediatric age groups, was selected and used to assess, visualize, and compare the overall predictive power of the 10 PBPK models for the different age groups (Figure 3).

In case of ratio comparison with calculated PK parameters such as AUC and clearance, when data were sparse, observed PK parameters were not derived through NCA of clinical data but from PopPK simulations. The PopPK estimates were assumed to adequately represent the actual PK of the respective study data.

All 27 estimated PK parameter ratios (100%) fell within a 2-fold error range, and 18 ratios (67%) fell within the bioequivalence range, indicating that the overall predictive performance of the pediatric PBPK models was adequate (Figure 3). The error in the predicted PK ratios appeared to increase as age decreased, but it also did not exceed the 2-fold error range in the youngest group. Among the investigated drugs, no bias for systematic over- or underestimation of the PK ratios was evident (Figure 4 and 5). Overall, these findings are comparable to those previously presented in a retrospective analysis on CYP-metabolized drugs using PK-Sim.[58]

For drugs eliminated exclusively via glomerular filtration (amikacin, gadovist, and magnevist), observed PK data were available for all 4 age groups, although not for every drug in each of these age groups (Figure 4). The comparison of the individual ratios of predicted to observed PK parameters for amikacin

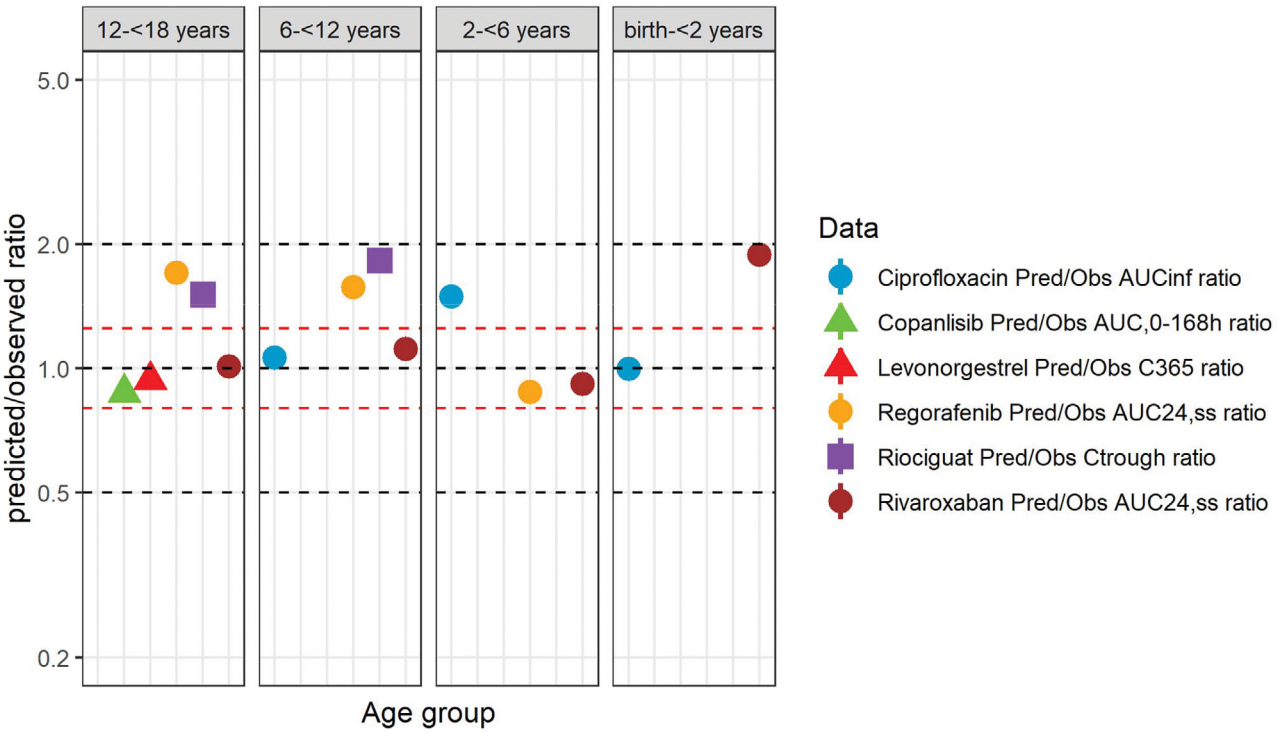

Figure 5. Ratios of predicted to observed secondary PK parameters for the evaluated drugs in different pediatric age groups. The age groups are sorted in descending order from adolescents (left) to neonates and infants (right). The different colors represent the different compound PK ratios. The different symbols represent the different PK parameters. Black dotted lines indicate 0.5, 1-, and 2-fold prediction intervals. Red dotted lines indicate 0.8- and 1.25-fold prediction intervals. $AUC_{0\text{-}168\ h}$, area under the concentration-time curve from time 0 to 168 hours; $AUC_{24,ss}$, area under the concentration-time curve from time 0 to 24 hours after the last dose in steady-state; AUC_{inf}, area under the concentration-time curve from time 0 to infinity; C_{365}, levonorgestrel concentration after 365 days; C_{trough}, trough concentration.

illustrated that passive elimination over the entire pediatric range was well described (Figure 2). Ontogeny of absorption, distribution, metabolism, and elimination processes implemented in PK-Sim were previously evaluated,[3,4,42] and are documented on the OSP GitHub website.[21] In the applied PBPK models, either only passive (renal) elimination or combined passive and active elimination was involved. In this analysis, the PBPK approach was successfully applied for the intended use as illustrated in Figure 4 using compounds developed by Bayer.

For most of the investigated compounds, total body clearance comprised several elimination pathways (eg, biliary clearance, metabolism via multiple enzymes), which lessens the suitability of using these drugs as marker compounds for the maturation of a specific clearance process. Additionally, for most of the compounds, not all active processes were known. In these cases, elimination was modeled partly via processes that were not fully characterized, for example, as metabolism without further specification of the responsible enzyme or TS mediated by an unknown efflux transporter. In doing so, the specific activity of the enzyme/transporter normalized to organ weight of the adult PBPK model was assumed to be unchanged in the pediatric model. Absolute clearance was then affected only by age-related changes in the weight of the organ where the process occurred (eg, liver or kidney), but not by additional maturation of the intrinsic clearance (eg, enzyme tissue concentration). The adequate predictive performance for these drugs corroborates the assumption that at least the major part of total clearance is not qualitatively different between children and adults, as this would have likely resulted in substantial over- or underestimation of a drug's PK ratio.

As not all possible active processes (eg, different transporters or other CYP substrates), or large molecule drugs were evaluated, additional studies for other compounds could further evaluate the predictive model performance in children. Especially in the youngest age group where the maturational changes are highest, and where, although predicted within 2-fold error range, the highest overestimation and underestimation of the observed PK parameter was observed (Figures 3–5). This could help to fill the knowledge gaps in ontogenies that were not addressed here, as reported elsewhere.[5] Additionally, a subcategorization

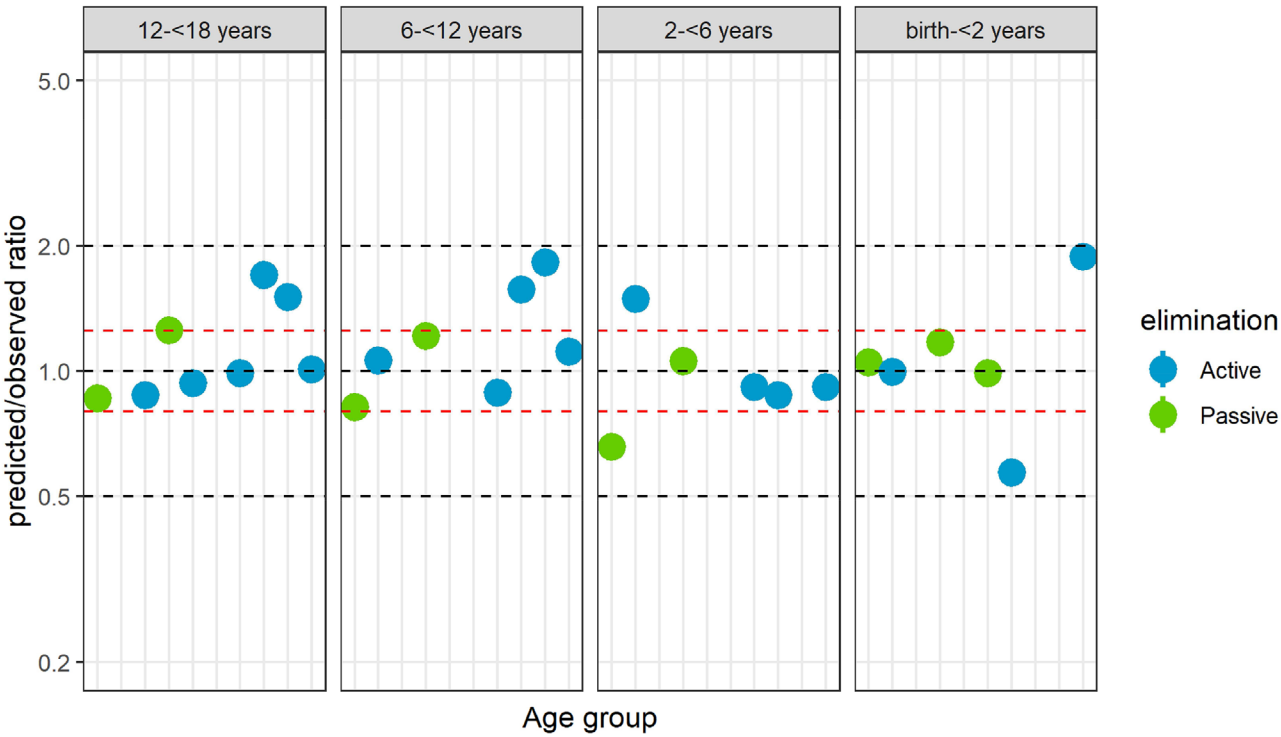

Figure 6. Ratios of predicted to observed PK parameters for the evaluated drugs in different pediatric age groups. The age groups are sorted in descending order from adolescents (left) to neonates and infants (right). The different colors represent all compounds with active (blue) or passive (green) elimination route. Black dotted lines indicate 0.5, 1-, and 2-fold prediction intervals. Red dotted lines indicate 0.8- and 1.25-fold prediction intervals.

of children <2 years of age, which are most affected by maturation, should be explored.

Although interindividual variability was included in the PBPK predictions, in this methodological study, the focus was set on the mean predictive performance of PBPK to support adequate dosing in pediatric clinical trials. As a next step, prediction of variability could be further investigated to not only cover the typical pediatric patient, but the full population range as shown exemplarily for amikacin (Figure 2).

The presented findings demonstrate that the confidence in pediatric PBPK models is generally reasonable for small-molecule drugs. Although oral absorption was not in the focus of the present analysis, a limitation of pediatric PBPK models is the lack of a fully mechanistic description of the processes pertaining to drug dissolution and absorption. Although numerous pediatric PBPK model for orally administered drugs can be found in the literature,[10] important knowledge gaps remain.[10,59] For the orally aministered compounds in this analysis (eg, rivaroxaban and ciprofloxacin) , dissolution was described by an empirical Weibull function with relevant parameters in this function being fitted in the adult PBPK model.[13,15] Typically, new (suspension) formulations need to be developed for children who cannot swallow the tablet given to adults (eg, for rivaroxaban and riociguat). For the majority of published models, the drug release kinetics implemented in the model were not reported, and specific oral dosage forms administered to children were rarely explicitly accounted for.

With the recently increasing interest in developing (semi)mechanistic models for drug dissolution and absorption,[60–62] many efforts are now directed at further improving dissolution and absorption modeling.[63,64] Adopting a more mechanistic approach to drug release in children, dissolution kinetics could be measured in vitro in biorelevant media that reflect the gastrointestinal physiology in children[65,66] and described using a (semi)mechanistic dissolution model, which is then integrated in a whole-body pediatric PBPK model.

Conclusions

This study presents a condensed experience of applying pediatric PBPK modeling to internally developed drugs for supporting important clinical decisions. The findings demonstrate that the PK of the 10 small-molecule compounds was adequately predicted in different pediatric age groups. This illustrates the predictive power of PBPK for guiding dosing schemes for compounds in the pediatric population. As a next step, a specific focus on the inclusion and description of variability

should be studied. Ultimately, thoroughly validated PBPK models for children could routinely support drug development programs, thereby catalyzing the speed, efficacy, and success rate of pediatric drug development.

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Conflicts of Interest

This work has not been published elsewhere. All co-authors are Bayer employees and potential stock owners. Some of the authors use Open Systems Pharmacology software in their professional role. There are no other arrangements of financial nature, or of any other kind, that could lead to conflict of interests with regard to this manuscript.

Disclosures

Bayer is fully committed to publicly disclose information about its clinical trials in humans. Public disclosure of clinical trial information is done in line with the position of the global pharmaceutical industry associations laid down in the "Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases". (For more information see https://clinicaltrials.bayer.com/transparency-policy.)

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