ORIGINAL RESEARCH ARTICLE

Clin Pharmacokinet 2006; 45 (10): 1013-1034
0312-5963/06/0010-1013/$39.95/0

Development and Evaluation of a Generic Physiologically Based Pharmacokinetic Model for Children

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Abstract

Background: Clinical trials in children are being encouraged by regulatory authorities in light of the immense off-label and unlicensed use of drugs in the paediatric population. The use of *in silico* techniques for pharmacokinetic prediction will aid in the development of paediatric clinical trials by guiding dosing regimens, ensuring efficient blood sampling times, maximising therapeutic effect and potentially reducing the number of children required for the study. The goal of this study was to extend an existing physiologically based pharmacokinetic (PBPK) model for adults to reflect the age-related physiological changes in children from birth to 18 years of age and, in conjunction with a previously developed age-specific clearance model, to evaluate the accuracy of the paediatric PBPK model to predict paediatric plasma profiles.

Methods: The age-dependence of bodyweight, height, organ weights, blood flows, interstitial space and vascular space were taken from the literature. Physiological parameters that were used in the PBPK model were checked against literature values to ensure consistency. These included cardiac output, portal vein flow, extracellular water, total body water, lipid and protein. Five model compounds (paracetamol [acetaminophen], alfentanil, morphine, theophylline and levofloxacin) were then examined by gathering the plasma concentration-time profiles, volumes of distribution and elimination half-lives from different ages of children and adults. First, the adult data were used to ensure accurate prediction of pharmacokinetic profiles. The model was then scaled to the specific age of children in the study, including the scaling of clearance, and the generated plasma concentration profiles, volumes of distribution and elimination half-lives were compared with literature values.

Results: Physiological scaling produced highly age-dependent cardiac output, portal vein flow, extracellular water, total body water, lipid and protein values that well represented literature data. The pharmacokinetic profiles in children for the five compounds were well predicted and the trends associated with age were evident. Thus, young neonates had plasma concentrations greater than the adults and older children had concentrations less than the adults. Eighty-three percent, 97% and 87% of the predicted plasma concentrations, volumes of distribution and elimination half-lives, respectively, were within 50% of the study reported values. There was no age-dependent bias for term neonates to 18 years of age when examining volumes of distribution and elimination half-lives.

Conclusion: This study suggests that the developed paediatric PBPK model can be used to scale pharmacokinetics from adults. The accurate prediction of pharmacokinetic parameters in children will aid in the development of dosing regimens and sampling times, thus increasing the efficiency of paediatric clinical trials.

Background

With the introduction of the US FDA Pediatric Exclusivity Provision in 1997,[1] there has been an increase in the number of paediatric trials requested by the FDA and conducted by the pharmaceutical industry.[2] The provision encourages the development of paediatric indications by offering 6 months of patent exclusivity for drugs in which paediatric clinical trials are completed. FDA and European authorities are aiming to increase the number of paediatric indications in light of the too few paediatric drugs available and the high off-label and unlicensed drug use in children. Approximately 50% of all drugs administered to children have not been tested in children, with the greatest percentage of off-label use (90% of all administered drugs) in those under 1 year of age.[2-4] The increased risk of adverse drug reactions from off-label and unlicensed drug use in children[5,6] will be reduced with label alterations inclusive of child-appropriate dosing and safety precautions.

Clinical trial development in children is burdened with both ethical and technical constraints.[7] Difficulties are encountered in gaining informed consent, taking blood and urine samples, ascertaining child-friendly equipment and procedures and in recruiting – especially for trials incorporating placebos.[7] Greater resources are thus required with a concomitant cost increase. With an understanding of the pharmacologically significant differences between adults and children using predictive simulation, paediatric clinical trials can be optimised through the guidance of dosing regimens and the planning of efficient sampling.[8] To underline the value of predictive simulation in drug approvals, the FDA presented case studies where pharmacokinetic prediction both reduced the number of children required for study and reduced the number of paediatric clinical trials necessary for labeling.[9] One type of predictive simulation is the use of physiologically based pharmacokinetic (PBPK) modelling.

This modelling technology employs a rigorous description of mass transport between the organs via the systemic circulation on the basis of known organ-related physiological parameters, such as organ volumes, blood flow rates and tissue composition information. In addition, substance-specific parameters such as organ/plasma partition ratios are required model parameters. An excellent review of the PBPK methodology, including organ-based equations for permeability and perfusion limited scenarios, and a discussion about the practical uses of PBPK models has recently been published.[10]

PBPK modelling is ideal for examining pharmacokinetic changes between adults and children of varying ages. Profile differences are due primarily to anatomical and physiological age-related changes, such as tissue compositions, relative organ weights, blood flow rates and the maturity of processes, such as renal or enzymatic function.[11-13] Based on body composition differences, the tissue distribution of compounds lead to different volumes of distribution reported for children and adults.[13] On the basis of maturity and physiological differences, clearance, a major driver of pharmacokinetic profiles, is also age dependent.[12,14,15] Using child-specific PBPK models that incorporate these age related differences, the pharmacokinetic profile of drugs in children can be predicted.[16,17]

The goal of this study was to extend an existing PBPK model for adults to reflect the age-related physiological changes in children from birth to 18 years of age and, in conjunction with a predicted age-specific clearance using clearance scaling methods as previously developed,[14] to evaluate the accuracy of the paediatric PBPK model to predict

Table I. Physico-chemical and protein binding parameters of test compounds

Compound	Lipophilicity	Molecular weight (g/mol)	Plasma unbound fraction [%] (major binding plasma-protein)	References
Paracetamol (acetaminophen)	0.46[a]	151.2	95 (albumin)	21,22
Alfentanil	2.1[a]	416.5	10 (α_1-acid glycoprotein)	21,23-25
Morphine	0.89[a]	285.3	75 (albumin)	21,26
Theophylline	−0.02[a]	180.2	55 (albumin)	21-23,27
Levofloxacin	0.9[b]	370.4	70 (albumin)	23,28,29

a Experimental log octanol/water partition coefficient.

b cLogP (polar/non polar solvent partition coefficient) calculated from compound structure.

paediatric plasma profiles. The potential use of this model in paediatric trial design and therapeutics will be discussed.

Materials and Methods

Physiologically Based Pharmacokinetic Modelling

PBPK simulations were carried out using the software PK-Sim® [1] (Bayer Technology Services GmbH, Leverkusen, Germany). PK-Sim® is a commercially available tool for PBPK modelling of drugs in laboratory animals and humans. In summary, PK-Sim® is based on a generic PBPK-model with 17 organs and tissues. Represented organs/tissues include arterial and venous blood, adipose tissue (separable adipose, excluding yellow marrow), brain, bone (including yellow marrow), gonads, heart, kidneys, large intestine, liver, muscle, portal vein, pancreas, skin, small intestine, spleen and stomach. Each organ consists of four sub-compartments, namely the plasma, red blood cells (which together build the vascular space), interstitial space and cellular space. Distribution between the plasma and red blood cells as well as between the interstitial and cellular compartments can be permeation limited. In the brain, the permeation barrier is located between the vascular and the interstitial space. PK-Sim® estimates model parameters (organ partition coefficients, permeabilities) from physico-chemical properties of compounds and from the composition of tissues in terms of lipids, water and protein.[18] The physico-chemical properties required as input information are molecular weight, lipophilicity and fraction unbound, and are presented in table I for the compounds used in this study. In addition to physico-chemical inputs, clearance values separated into renal and hepatic elimination were required. For a detailed description of the PBPK model structure implemented in PK-Sim®, see Willmann et al.[18,19] or the software manual.[20]

Collection of the Relevant Physiological Parameters in Children

Information regarding the age dependencies of the relevant physiological parameters in children was gathered from the literature. Bodyweight, height and organ weights/volumes were taken from the International Committee on Radiological Protection (ICRP) publication.[30] This publication was previously used to gather the same information for adults. The sum of the weights of all organs included in the PBPK model amounted to 91–93% of the total age-specific bodyweight. This was caused by some organs, such as the thyroid and adrenals, not being accounted for in the model. Instead of using an 'other' compartment, which would not have a physiological basis, all accounted organ weights were increased proportionally to sum to total bodyweight.

Age-dependent blood flows for brain,[31-34] kidney,[35-37] muscle[38-41] and skin[40,42-45] were taken from various literature sources. Because data on age-specific blood flows were lacking for the remaining organs, we assumed the same percentage of cardiac output as is reported for adult organs[30,46] in these cases. Hepatic blood flow (Q_H) was the addi-

1 The use of trade names is for product identification purposes only and does not imply endorsement.

tion of portal plus arterial flow. The pre-portal organs, including the intestines, pancreas, spleen and stomach, regulate portal blood flow and comprise approximately 75% of total Q_H. Blood flows to the pre-portal organs were scaled by cardiac output (as reported in ICRP[30]) and were compared with literature values for total portal blood flow in children.[47-50] The arterial contribution to Q_H in children was scaled maintaining the same blood flow per gram of liver as in adults. Since the sum of all blood flows should equal cardiac output, the sums were compared with literature values of age-specific cardiac outputs.[50-58]

Age-dependent changes in tissue compartmentalisation and composition were also considered. As previously defined in PK-Sim® for adults, the vascular space of each organ was calculated from its blood content, taken as a percentage of total blood volume in adults.[46] Adjustments were made to the stomach, small intestines and large intestines where 75% of their total blood content was attributed to the portal vein and 25% was considered as vascular space. Two-thirds of the vascular space in the liver was attributed to the liver and the remainder was attributed to the portal vein.[49] For the scaling of organ vascular space in children, the proportion of blood content in adult organs was maintained since there was no evidence of their age-dependence. Values for the interstitial space in organs were gathered from the literature[49,59-64] and were already implemented in the PBPK model for adults. There was, however, evidence that the interstitial space in some organs is age-dependent. The fraction of adipose[61,64] and muscle[62] interstitial space has been observed to be greater in neonates and young infants compared with adults. This age-dependence in interstitial space was included in the PBPK model and was also accounted for by way of the relative changes of protein, lipid and water fractions. Organ composition values that were previously input into PK-Sim® for adults,[30,65,66] were maintained for children with the exception of adipose tissue being adjusted for the age-dependence of water and lipid levels,[61,64] and muscle tissue adjusted for the age-dependence of water and protein levels.[62] Vascular and interstitial spaces in the organs of adults and children are presented in table II.

Cubic splines of parameter values (e.g. Q_H, blood volume, height) versus age were used to interpolate between discrete ages using MATLAB version 7.0 (Mathworks, MI, USA). Splines were used because literature values for the parameter values were only available for certain ages, while continuous age-dependence was needed for the simulations. The age-dependence of organ volumes, blood flow rates and tissue composition were stored in a database and implemented in PK-Sim®. Thus, upon input of the individual's sex, age, and bodyweight/height relation, the parameter values were automatically generated and used in the PBPK model.

Table II. Fraction of vascular and interstitial space in the human organs[16,49,59-64]

Organ	Vascular space	Interstitial space
Adipose	0.18	
0y		0.54
1y		0.35
5y		0.35
10y		0.23
15y		0.22
30y		0.16
Brain	0.039	0.004
Gonads	0.055	0.07
Heart	0.14	0.1
Kidneys	0.23	0.2
Large intestine	0.06	0.094
Liver	0.17	0.163
Lung	0.58/0.53[a]	0.188
Muscle	0.025	
0y		0.44
1y		0.32
5y		0.28
10y		0.24
15y		0.18
30y		0.16
Pancreas	0.2	0.12
Skeleton	0.034	0.1
Skin	0.046	0.3
Small intestine	0.05	0.094
Spleen	0.33	0.15
Stomach	0.06	0.1

a Male/female.

To check the consistency of the resulting physiological parameters in children, the resulting total blood content, total extracellular and body water, and total lipid and protein content were calculated and compared with reported literature values. The total blood content[30] was determined by adding the vascular fractions of all organs, plus the volume of the blood vessels, including the portal vein. Extracellular water[67-69] was calculated as the sum of all interstitial spaces, plasma volume and the contents of the gastrointestinal tract. Total body water, lipid and protein content[67-73] were also summed for all organs.

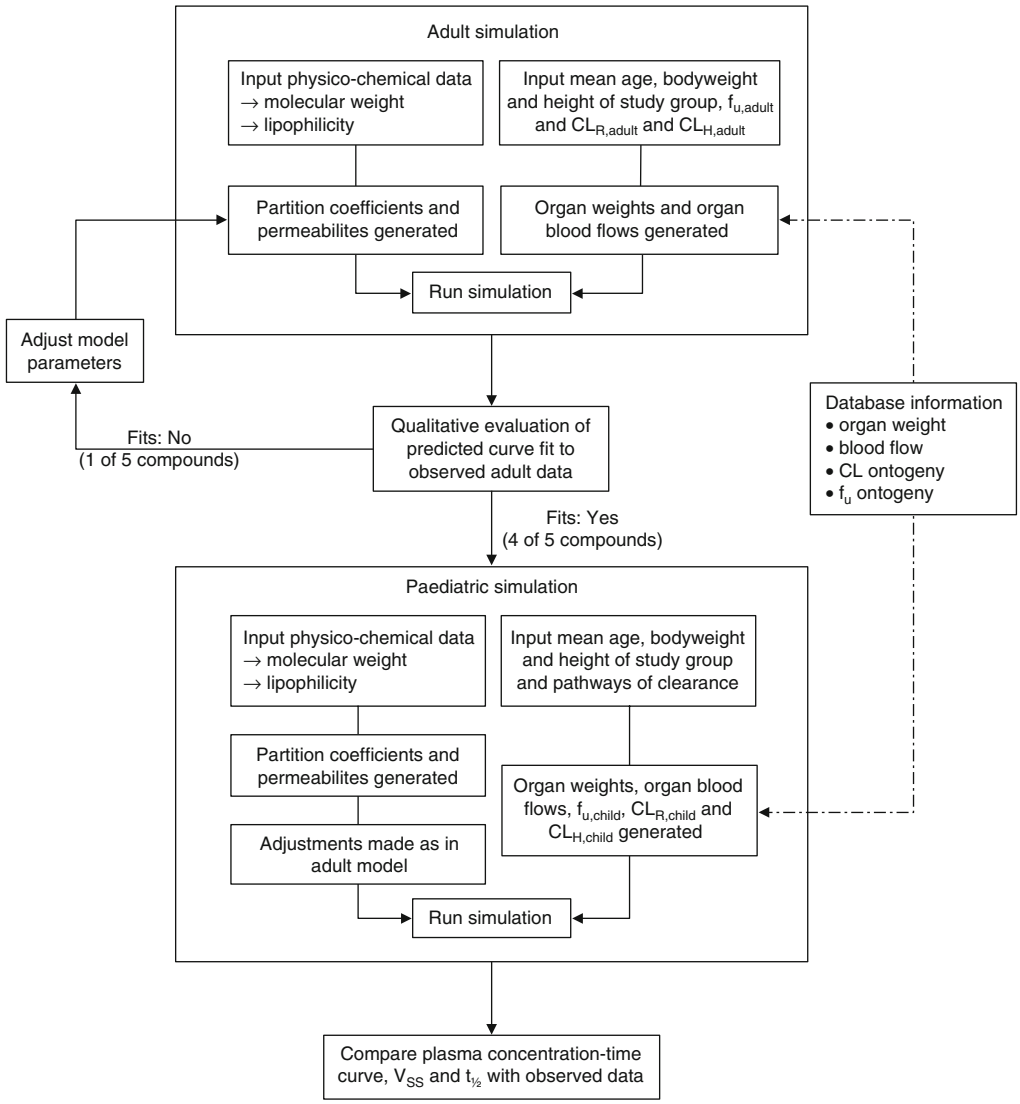

Fig. 1. Work-flow schematic of the process used to predict the pharmacokinetics of five compounds in children of different ages. $CL_{R,adult}$ and $CL_{R,child}$ are renal clearances in adults and children, respectively. $CL_{H,adult}$ and $CL_{H,child}$ are hepatic clearances in adults and children, respectively. The fraction unbound in adults and children are represented by $f_{u,adult}$ and $f_{u,child}$, respectively. $t_{½}$ = elimination half-life; V_{ss} = apparent volume of distribution at steady state.

Pharmacokinetic Data for Adults and Children

To evaluate the performance of the PBPK model, the pharmacokinetic literature was searched for compounds in which both adult and children concentration-time data, following administration via bolus or short-term intravenous infusion, were available. Studies were selected only if the observed plasma concentration data were presented as numerical values or graphs with observed data. Only mean plasma concentration-time data were graphed and

Table III. The ratio of predicted unbound fraction in children ($f_{u,child}$) to the reported unbound fraction in adults ($f_{u,adult}$) in plasma and tissue : plasma partition coefficients, as predicted from physico-chemical properties in PK-Sim®[a]

Parameter	Paracetamol (acetaminophen)	Alfentanil[b]	Morphine	Theophylline	Levofloxacin
$f_{u,child}/f_{u,adult}$					
0y	1.01	1.7	1.06	1.14	1.08
1y	1	1.6	1.05	1.12	1.07
5y	1	1.3	1.04	1.06	1.04
10y	1	1	1.01	1.02	1.01
15y	1	1	1	1	1
30y	1	1	1	1	1
Adipose : plasma					
0y	1.63	4.98	2.70	0.47	2.57
1y	2.01	7.60	3.77	0.47	3.59
5y	2.01	7.60	3.77	0.47	3.59
10y	2.23	9.10	4.38	0.46	4.18
15y	2.24	9.23	4.43	0.46	4.22
30y	2.37	10.10	4.78	0.46	4.57
Brain : plasma	1.10	1.49	1.27	0.46	1.20
Gonads : plasma	0.88	0.51	0.81	0.43	0.76
Heart : plasma	1.02	1.38	1.17	0.43	1.11
Kidneys : plasma	0.92	0.78	0.93	0.43	0.87
Large intestine : plasma	0.96	0.90	0.99	0.44	0.93
Liver : plasma	0.95	1.00	1.01	0.42	0.95
Lung : plasma	0.84	0.26	0.71	0.43	0.66
Muscle : plasma					
0y	0.90	0.29	0.76	0.45	0.71
1y	0.86	0.29	0.73	0.43	0.69
5y	0.85	0.30	0.73	0.43	0.68
10y	0.85	0.30	0.73	0.43	0.68
15y	0.85	0.30	0.73	0.43	0.68
30y	0.85	0.30	0.73	0.43	0.68
Pancreas : plasma	0.93	1.12	1.03	0.41	0.97
Bone : plasma	1.25	3.50	1.98	0.39	1.88
Skin : plasma	0.93	1.40	1.11	0.38	1.05
Small intestine : plasma	0.96	0.90	0.99	0.44	0.93
Spleen : plasma	0.83	0.34	0.73	0.41	0.68
Stomach : plasma	0.96	0.90	0.99	0.44	0.93

a The age-specific partition coefficient is the product of the ratio of unbound fraction and the partition coefficient. The age dependence is given explicitly only for adipose and muscle because it is additionally influenced by tissue composition. In all other cases the relative age dependence is the same as for $f_{u,adult}/f_{u,child}$.

b The partition coefficients used in the physiologically based pharmacokinetic model for alfentanil were reduced by a factor of 20 from the predicted partition coefficients.

compared with the predicted values with the knowledge that there was variability in literature-reported mean pharmacokinetic plasma concentration-time data at all ages. As a result of this survey, five compounds were selected for this study: paracetamol (acetaminophen), alfentanil, morphine, theophylline and levofloxacin.

Work Flow for Simulations in Children

Figure 1 represents the work flow for the paediatric PBPK simulations. First, the adult pharmacokinetic profile following intravenous administration was simulated after inputting the physico-chemical compound parameters (table I): the mean bodyweight, height and age of the studied group and the mean reported clearance value. Based on the physico-chemical compound inputs, compound-specific partition coefficients were generated. These are presented in table III. The simulation was performed and the simulated plasma concentration-time curve was superimposed onto the mean observed data and assessed qualitatively for accuracy (see the next section 'Assessment of Appropriateness of the Simulation'). Observed data for adults was taken from the following studies: paracetamol,[74,75] alfentanil,[76,77] morphine,[78,79] theophylline[80,81] and levofloxacin.[82]

When the simulated curves in adults matched the observed data with sufficient accuracy, the mean age, height, and bodyweight were changed according to the reported data of the paediatric study group. In addition, the dosing regimen, clearance and predicted age-dependent protein binding, as calculated from the equations in McNamara and Alcorn[83] (table III), were input. A predicted value for clearance in children was generated using the scaling method previously described by Edginton et al.[14] For all but levofloxacin, the age-dependence of clearance has been previously calculated.[14] As an example, the derivation of the age-dependence of levofloxacin clearance is described in the Results section. No further changes to any other input parameters were allowed in the model during the simulations in children. In the simulations, the time at which the plasma monitoring stopped was the last timepoint simulated in the PBPK model.

The simulated plasma concentration-time curves for children were then superimposed onto observed values. To examine the importance of accurate clearance prediction in the assessment of plasma concentration-time curves in children, all simulations were performed using the clearance value as reported in the study and the predicted clearance value. For simulations using the reported clearance value, the volume of distribution at steady state (V_{ss}) and elimination half-life were calculated and compared with literature values. V_{ss} was calculated using equation 1:

$$V_{ss} = MRT \bullet CL \quad \text{(Eq. 1)}$$

where CL was total clearance (L/h/kg) and MRT was the mean residence time calculated using equation 2:

$$MRT = \frac{AUMC}{AUC} - \frac{TI}{2} \quad \text{(Eq. 2)}$$

where AUMC was the area under the moment curve, AUC was the area under the plasma concentration-time curve and TI was the infusion time. Elimination half-life was calculated from the last 10% of the simulated data points of the plasma concentration-time curve.

Assessment of Appropriateness of the Simulation

In accordance with Holford et al.[84] for good simulation practices, the PBPK model evaluation was based on three measures. These include:

- mechanistic evaluation where the underlying physiological data and processes (e.g. cardiac output, total body water) were compared with literature values;
- empirical evaluation where predicted pharmacokinetic parameters and curves were compared with literature values;
- numerical evaluation of the predictivity of the model.

Bias for the observed versus predicted plasma concentration values, V_{ss} and elimination half-lives

Table IV. Organ blood flows, portal blood flow, total hepatic blood flow (Q_H), bodyweight and height used in the physiologically based pharmacokinetic model[30-50]

Parameter	Newborn	1y	5y	10y	15y	Adult (30y)
Organ blood flow (mL/min)						
adipose	30	12	171	250	315/484[a]	325/502[a]
brain	180	700	900	840/750[a]	805/708[a]	780/708[a]
gonads	0.3	0.6	1.7/0.7[a]	2.5/1.0[a]	3.2/1.1[a]	3.3/1.2[a]
heart	24	48	136	200	252/285[a]	260/295[a]
kidneys	110	230	577	854	1335/950[a]	1325/1120[a]
large intestine	24	48	136	200	251/285[a]	260/295[a]
liver	39	78	221	325	409/370[a]	423/383[a]
muscle	31	72	212	429	941/646[a]	1105/665[a]
pancreas	6	12	34	50	63/57[a]	65/59[a]
skeleton	30	60	170	250	315/285[a]	325/295[a]
skin	30	60	170	250	315/285[a]	325/295[a]
small intestine	60	120	340	500	630/627[a]	650/649[a]
spleen	18	36	102	150	189/171[a]	195/177[a]
stomach	6.0	12	34	50	63/57[a]	65/59[a]
Portal blood flow (mL/min)	114	228	646	950/950[a]	1197/1197[a]	1235/1239[a]
Q_H (mL/min)	153	306	867	1275/1273[a]	1600/1566[a]	1660/1620[a]
Bodyweight (kg)	3.5	10	19	32	56/53[a]	73/60[a]
Height (cm)	51	76	109	138	167/161[a]	176/163[a]

a Male/female.

were assessed as described in Sheiner and Beal.[85] Accuracy of the predictions was assessed using the absolute percentage error, i.e. the difference between the observed and predicted values, as a percentage of the observed value. Here, the focus was on the proportion of predicted values that differed no more than 30% and 50% from the observed values. Values derived from premature neonates were excluded from the bias and accuracy measures. For each individual curve, a mean relative deviation (MRD) was calculated and is defined as the average distance of the observed plasma concentration values from the predicted values on a logarithmic scale (equation 3):

$$MRD = 10^{x} \; ; x = \sqrt{\frac{\sum_{i=1}^{n}(\log y_i - \log \hat{y}_i)^2}{n}} \quad \text{(Eq. 3)}$$

where, $\log y_i$ is the logarithm of the observed plasma concentrations, $\log \hat{y}_i$ is the ith logarithm of the predicted plasma concentrations and n is the number of observed values. An MRD value of ≤2 (meaning that the average of the predicted values is equal to or less than a factor of 2 from the observed values) was considered a reasonable prediction.

Results

Summary of Physiological Parameters in Children

Age-dependent bodyweight and height as well as organ blood flows are presented in table IV. Q_H was the addition of the pre-portal blood flows plus the liver arterial blood flow (table IV). The addition of the pre-portal organ blood flows generated age-dependent total portal blood flows similar to literature values (table IV). Since portal blood flow is approximately 75% of the total Q_H,[30] this suggested that the age-dependence of Q_H was adequately represented. The addition of all blood flows should equal cardiac output. Cardiac output values used in

the PBPK model were similar to literature values for children (table V).

Other checks for consistency included examining the total blood volume, total blood water, extracellular water and total lipid and protein used in the PBPK model compared with literature values. The addition of venous blood, arterial blood, portal vein blood and all organ blood volumes (vascular space; table II) adequately represented the age-dependent total blood volume in females and males (table VI and table VII). The addition of the interstitial space (table II) plus the gut contents and blood plasma volume was similar to reported values for extracellular water in all age groups and was gender dependent (table VI and table VII). The calculated values for total body water, total body lipid and protein matched reasonably well to those found in the literature (table VI and table VII).

Table V. Reference values for the age-dependence of cardiac output, compared with those used in the physiologically based pharmacokinetic model in the present study

Age range	Mean age	Cardiac output (L/min) [mean ± SD]	Reference
3–27d	5d	0.50 ± 0.12[a]	51
2wk–2mo	NR	0.68 ± 0.13[a]	52
2.1–4.4mo	NR	0.93 ± 0.11[a]	
4.5–7.5mo	NR	1.1 ± 0.24[a]	
7.6–10.5mo	NR	1.3 ± 0.26[a]	
10.6–13.5mo	NR	1.5 ± 0.33[a]	
6mo–14y	5.6y	3.9 ± 0.95[a]	53
6mo–14y	5.4y	3.2 ± 0.80[a,b]	54
5–15y	9.4y	3.9 ± 0.1[b]	55
7–9y	NR	4.8/4.3[c]	56
10y	10y	4.4/6.2[c]	
11y	11y	4.4/5.9[c]	
12y	12y	5.7/4.8[c]	
NR	13y	4.4 ± 0.73 (all male)[a]	57
12.4 ± 4.5y	12.4y[d]	4.0 ± 1.1	58
13y	13y	5.3/6.1[c]	56
14y	14y	7.1/7.4[c]	
15y	15y	6.6/7.0[c]	
16–19y	NR	7.3/7.2[c]	
22–67y	42y	5.8 ± 0.3	50
All ages	Newborn	0.6	30
	1y	1.2	
	5y	3.4	
	10y	5.0	
	15y	6.1	
	Adult	6.5/5.9[c]	
All ages	Newborn	0.59	Present
	1y	1.5	study
	5y	3.2	
	10y	4.4/4.3[c]	
	15y	5.9/5.2[c]	
	Adult	6.1/5.5[c]	

a Presented in the original paper as mL/min/m^2. Boyd[86] method of body surface area was used to recalculate cardiac output to L/min.

b Values from control patients.

c Male/female.

d Patients were examined, on average, 5.9y following a heart shunt operation.

NR = not reported.

Levofloxacin Clearance Prediction

Levofloxacin clearance scaling was not previously described in Edginton et al.,[14] whereas clearance scaling was described therein for all other compounds. As an example, the required inputs for the clearance scaling models[14] are listed here for levofloxacin. Based on information in adults, 80% of levofloxacin clearance was attributed to renal clearance (glomerular filtration and tubular secretion),[23] 10% to biliary clearance and 10% to hepatic clearance via glucuronidation.[87] Levofloxacin is enzymatically cleared via uridine diphosphate glucuronosyltransferase (UGT) 1A1, UGT1A3 and UGT1A9[87] and ontological information was used for UGT1A1, where adult activity levels were reached by 6 months of age.[88] Levofloxacin clearance prediction followed the trend of increased weight-normalised clearance in young children in comparison with older children and adults (figure 2). Mean observed clearances were within 28% of the predicted clearances.

Evaluation of Pharmacokinetic Data in Children

In the cases of paracetamol,[89-91] morphine,[92,93] theophylline[94-96] and levofloxacin[82] the simulated plasma concentration-time curves accurately matched the data experimentally observed in adults. In the case of alfentanil, the simulated curve on the basis of the reported lipophilicity measure did not

Table VI. Total blood volume, total body water, extracellular water and total body lipid and protein in females as calculated from the physiological data in the physiologically based pharmacokinetic model in the present study compared with the reported values in literature

Age (y)	Total blood volume (mL)		Total body water (% BW)		Extracellular water (% BW)		Total lipid (% BW)		Total protein (% BW)	
	calculated	reported	calculated	reported	calculated	reported	calculated	reported	calculated	reported
Newborn	273	270[30]	67	75;[67] 72[73a]	37	40[67]	16	13[73a]	12	12[73a]
1	651	500[30]	57	60[67]	29	25[67]	27		12	13[71b]
5	1368	1400[30]	59	54;[71] 61[67]	27	22[67]	22		14	15[71b]
10	2290	2400[30]	57	59;[67] 57[68]	23	20;[67] 22[68]	23		14	15[71b]
15	4065	3300[30]	53		21		27		15	
30	5172	3900[30]	50	54;[72] 50[67]	19	18[67]	30		14	

a Experimental data using the mean of neonates with gestational ages of 38–42 weeks.

b Values not experimentally derived.

BW = bodyweight.

accurately describe the experimentally observed data in adults (data not shown). All organ partition coefficients were proportionally changed by a factor of 20 to match the simulated adult curve to the observed adult data. This adjustment was subsequently used for the partition coefficients in the alfentanil PBPK model for children.[97-99]

MRDs for the simulations in children were, on average 1.6 (table VIII), using either the reported clearance or the predicted clearance. In other words, the predicted plasma concentration-time values were, on average, within a factor of 1.6 from the observed values. There was slight bias towards underprediction when examining the plasma concentration-time data from the data using both the reported (−0.303 mg/L; 95% CI −0.511, −0.100) [figure 3a] and predicted clearance (−0.215 mg/L; 95% CI −0.426, −0.00332) [figure 3c] in the simulations. The bias was slightly less when the predicted clearances were used in the simulations. Precision for the simulations using the reported and predicted clearance values were similar with 80% and 83% of the predicted values being within 50% of the observed values, and 59% and 63% within 30%, respectively. For premature neonates, there was bias towards overprediction when the reported clearances and the predicted clearances were used. For term neonates to 18 year olds, with the exception of the underprediction for the one study using 1-day-old neonates, there appeared to be no age-related bias using the study-reported clearance values (figure 3b). For neonates aged over a few days, no age-related bias was evident using the predicted clearance values (figure 3d). This suggests that the clearance prediction overestimated clearance in neonates of a few days of age.

The PBPK model, in conjunction with age-related clearance scaling, accurately predicted the trends with age: premature and term neonates had plasma concentrations higher than those in adults, and older children had plasma concentrations lower than those in adults (see two example compounds in figure 4 and figure 5). Figure 4 represents the observed and predicted plasma concentration-time curves for alfentanil. For the simulations using the reported

Table VII. Total blood volume, total body water, extracellular water and total body lipid and protein in males as calculated from the physiological data in the physiologically based pharmacokinetic model in the present study compared with reported values in literature

Age (y)	Total blood volume (mL)		Total body water (% BW)		Extracellular water (% BW)		Total body lipid[a] (% BW)		Total protein (% BW)	
	calculated	reported	calculated	reported	calculated	reported	calculated	reported	calculated	reported
Newborn	267	270[30]	67	75;[67] 71[73]a	36	40[67]	16	13[73]a	12	13[73]a
1	635	500[30]	57	60[67]	28	25[67]	27		12	13[71]b
5	1335	1400[30]	59	61[67]	26	22[67]	22		14	16[71]b
10	2233	2400[30]	57	59;[67] 57;[68] 65[70]	22	20;[67] 22[68]	21	13.4[70]b	15	17[70]b
15	3321	4500[30]	60		20		18		16	
30	3833	5300[30]	58	61;[72] 59;[69] 61[67]	18	21;[69] 17[67]	21		16	

a Experimental data using the mean of neonates with gestational ages of 38 to 42 weeks.

b Values not experimentally derived.

BW = bodyweight.

clearance (figure 4a), the clearance used from Meistelman et al.[98] appears to be too low. Using the predicted clearance (figure 4b), the simulated curve well represents the observed data.

No bias was observed when the reported volumes of distribution (table IX) for term neonates to age 18 were plotted against the predicted values (−0.078 L/kg; 95% CI −0.183, 0.0272) [figure 6a]. Based on figure 6b, there appeared to be no bias with age. For volumes of distribution, 97% of the predicted values were within 50% of the reported values and 86% were within 30% of the reported values. There was bias towards overprediction in the predicted elimination half-life for term neonates to age 18 (0.45 hours; 95% CI 0.209, 0.706) [figure 6c]. Based on figure 6d, the bias towards overprediction appeared to be similar at all ages. For elimination half-life, 87% of the predicted values were within 50% of the reported values and 77% were within 30% of the reported values.

Discussion

Accurate physiologically based models must represent, to the best of the current knowledge, the physiological attributes of the simulated individual. Age-dependent mean bodyweight, height and organ weights were relatively easy to obtain. A comprehensive assessment of the ICRP[30] information source has been discussed by Bjorkman.[16] The age-dependence of organ blood flows was more difficult to locate and other sources were searched. Blood flows to the kidney,[35-37] muscle,[38-41] skin,[40,42-45] brain[31-34] and portal vein[47-50] were gathered from the literature and represented those compartments for which research had been undertaken at different ages. Using the literature-based age-specific kidney, muscle and brain blood flows, continuous functions were generated. Skin blood flow values were also available in the literature, but were highly inconsistent.[40,42-45] This is likely because of the sensitivity of this organ to perturbation and altered external conditions, such as crying, sleeping or feeding[40] and temperature.[43] Therefore, the age-dependent blood flows to this organ were also scaled using the percentage cardiac output method resulting in most

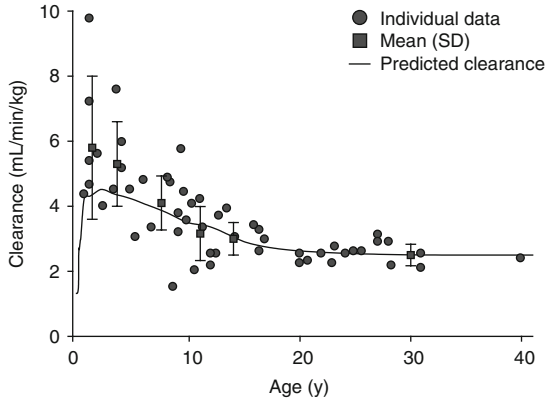

Fig. 2. Clearance as a function of age following levofloxacin intravenous administration to children and adults. The mean (SD) of the reported age ranges (0.5–2, 2–5, 5–10, 10–12, 12–16 years) and the individual data are presented in Chien et al.[82] The line denotes the predicted age-dependence of clearance for levofloxacin using the method of Edginton et al.[14]

of the literature values being adequately represented (table IV) [for comparison with literature values see references[40,42,43,45]]. Sufficient information was not available for other organs; thus, blood flows were assumed to be the same percentage of cardiac output as reported for adults.[30] Overall, values for organ blood flows were similar to those of Bjorkman[16] who, for the most part, scaled blood flows based on maintaining the same flow per gram tissue as in adults. For all ages, the sum of the organ blood flows should equal the total volume of blood pumped per unit time, which was demonstrated in the current study (table V) and closely resembled the cardiac outputs used by Bjorkman.[16]

The composition of each organ in terms of protein, water and lipid levels is important for the prediction of organ partition coefficients.[18,66] Levels of protein, water and lipid in most organs were taken directly out of ICRP.[30] It is assumed that these levels, except in the case of adipose and muscle tissue where other sources of literature were available, were the same between children and adults. Total body composition of protein and lipid is difficult to obtain in humans since only invasive means of measurement can be performed. Data for adults or older children were not available; however, based on limited data, the organ compositions seemed to adequately predict protein and lipid content in the term neonate (table VI and table VII).

Other physiologically relevant sums that should be well represented in a PBPK model are extracellular water and total body water. The calculation of these parameters from the PBPK model well represented literature data. Patterns were observed where neonates at birth had high extracellular water (37%) and total body water (67%) with a concomitant decrease in adiposity (16%) because of the age-dependence of adipose interstitial space. Water content declined with age, whereas total body lipid was both nonlinear with age and was dependent on the sex. These age-dependent changes are important for the accurate prediction of partition coefficients and volumes of distribution in children. The extent of the age-dependent differences in adipose and muscle interstitial space was similar (table II). However, their effect on partition coefficients differed greatly (table III). Although the muscle partition coefficients in children were within 5% of the adult values, the age-dependence of the adipose partition coefficients varied greatly, depending on the lipophilicity of the compound. In the case of the most hydrophilic compound (theophylline), there was almost no age-dependence of the adipose partition coefficients. In the case of more lipophilic compounds, the adipose partition coefficient differences reached up to a factor of 2 between adults and neonates. In adipose, this was because of the interplay between fat and water, where an increase in interstitial space (water) led to a decrease in fat content. In contrast, for muscle, the interplay was between water and protein. In addition, there was a

Table VIII. Combined mean relative deviations (MRDs) for the simulations in children and adults using the reported clearance and the predicted clearance

Drug	MRD	
	reported clearance	predicted clearance
Paracetamol (acetaminophen)	1.45	1.36
Alfentanil	2.07	1.50
Morphine	1.70	2.06
Theophylline	1.19	1.26
Levofloxacin	1.42	1.37
Average MRD	**1.60**	**1.57**

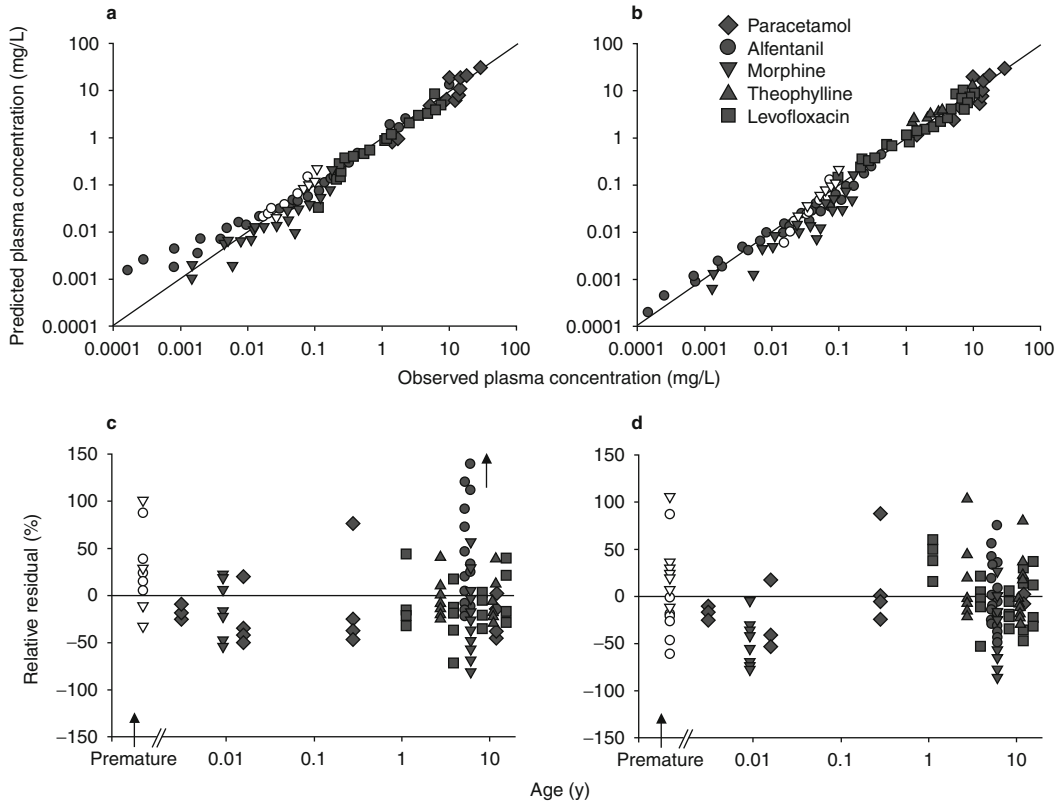

Fig. 3. Observed vs predicted plasma concentration data. (**a**) Predicted values derived using the study reported literature value clearance; and (**b**) predicted values derived using the predicted clearance value, for paediatric studies using paracetamol (acetaminophen), alfentanil, morphine, theophylline and levofloxacin. Open symbols represent data from premature neonates. (**c**) The relative residuals ([predicted value – observed value]/observed value × 100) vs age for the data in (**a**). (**d**) The relative residuals vs age for the data in (**b**). The arrow in (**c**) indicates that four additional relative residuals for alfentanil, at the age of 5.4 years, are within the dataset (254%, 431%, 816%, 818%), but were not presented for visual purposes.

countering effect of the unbound fraction between children ($f_{u,child}$) and adults ($f_{u,adult}$); the greater the $f_{u,child}/f_{u,adult}$, the lower the influence of the muscle and adipose interstitial space differences on the partition coefficients. In summary, taking into account the age-dependent physiological differences that are relevant for physiologically based modelling, a generic *a priori* paediatric PBPK model was developed.

Evaluation of the paediatric PBPK model was based on a novel approach using adult data as a reference point. First, the adult data were simulated based on the available literature on physico-chemical parameters. For four of the five compounds studied, this input was all that was required to accurately simulate the observed adult data. Adjustment to the adult model was required only if the curve shape did not match the observed data, as was the case for one of the five compounds (alfentanil). Initial curves for this compound were within the correct concentration region, but the curve shape deviated from the experimentally observed shape. This finding can be interpreted as a misestimation of the distribution parameters rather than a clearance issue. Consequently, the partition coefficients were manually adjusted to fit the adult plasma concentration-time data. The same adjustment was carried through to the paediatric model. It is our experience that a good representation of adult plasma data carries through to accurate simulations in children and

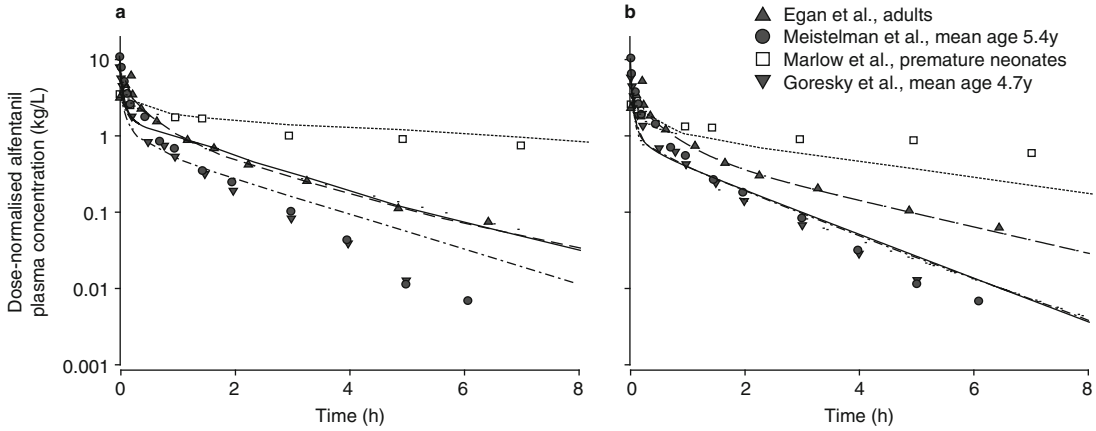

Fig. 4. Predicted dose-normalised plasma concentration-time curves (lines) for alfentanil administration to children. Either the study reported clearance (**a**) or the predicted clearance (**b**) was used as input for the physiologically based pharmacokinetic model. Observed concentration values (symbols) were taken from the literature: Mean age 5.4 years from Meistelmans et al.;[98] premature neonates from Marlow et al.;[99] and mean age 4.7 years from Goresky et al.[97] The adult data from Egan et al.[76] are presented for reference.

thus, by ensuring an accurate simulation of adult data, the confidence of the paediatric simulation accuracy increases.

PBPK models have been developed by other researchers (Bjorkman[16] for theophylline and midazolam; Ginsberg et al.[17] for caffeine and theophylline) to simulate compound pharmacokinetics in children. The major difference between all other paediatric PBPK models and that implemented in PK-Sim® is the source of the partition coefficients. In other models, experimental partition coefficients from animals are extrapolated to humans. Partition coefficients in PK-Sim® are predicted from physico-chemical parameters and have been demonstrated to be in good agreement with experimental data.[18] Another difference is the work-flow for the extrapolation of adult PBPK models to paediatric models. When *in vivo* adult pharmacokinetic data become available in phase I trials, the work-flow for extrapolation to paediatric PBPK models, as described herein, will increase the confidence of the paediatric pharmacokinetic predictions.

For all compounds investigated here, the trends of higher plasma concentrations in premature and term neonates and the lower plasma concentrations in older children, compared with adults, were evident for all compounds. Our model was reasonably precise over the entire concentration range, although it was evident that the precision was lower for some studies using morphine and alfentanil. This was because of two particular morphine studies, one in neonates aged 2 days[92] and the other in children aged 5.5 years,[93] where the mean observed plasma concentration-time values had great variability (see figure 5). In the alfentanil study,[98] the reported clearance value was incorrectly calculated leading to a deviation in predicted versus reported clearance values (see figure 4). Bias was low and tended towards slight underprediction of plasma concentrations. There appeared to be no age-related bias for neonates over a few days of age. The bias towards underprediction of plasma concentrations in neonates under a few days of age was evident and based on only two studies. The reasons for this are unknown, since the resulting volumes of distribution and elimination half-lives for these two studies were within 22% of the reported values. Unfortunately, there were not more *in vivo* plasma concentration data to thoroughly investigate this trend in very young neonates. Our assessment criteria were knowingly subjective. An *a priori* criteria for evaluating a simulation of plasma concentration-time curves is wholly dependent on the reasons for the simulations (e.g. determining efficient sampling points prior to clinical studies) and the allowable error (e.g. low for

narrow therapeutic range drugs) for the given application.

Also generated from the paediatric simulations were volume of distribution and elimination half-lives. Substantial variability in volumes of distribution, at any age, was evident from our literature search (table IX). Mean volumes of distribution at all ages, except premature neonates, were well described by the model, with 97% and 86% of the values deviating <50% and <30%, respectively, from the reported values (see also figure 6). Furthermore, the extent and direction of the age-dependent change in volume of distribution, caused by age-dependent physiological changes, were captured by our model (table IX). While not readily seen in the literature data, because of the great variability among studies and within individuals of a study, it was well described for morphine in three studies[103-105] (table IX). Most likely, any deviations from the mean observed plasma concentrations were a result of the over- or underprediction of clearance, not volume of distribution. One of the strengths of using the PBPK modelling approach over conventional compartmental model scaling is the ability to determine curve shape in children, which is related to the volume of distribution. Commonly, adult compartmental models (e.g. two or three compartmental models) are used for predicting pharmacokinetics in children using a scaled volume of distribution and clearance. This assumes that the number of compartments is the same across individuals of different ages. However, because of the interplay between body composition differences in humans of different ages and compound-specific properties, this is not necessarily the case. PBPK models take into account both of these aspects and can detect curve shape changes in children compared with adults.

For the simulated elimination half-lives, there was bias towards overprediction. However, the accuracy was quite good with 87% and 77% of predicted values deviating <50% and <30%, respectively, from the reported values. Experimental elimination half-lives are calculated, in all nonlinear regression packages, from the terminal slope of the line within a user-defined time interval. The interpolation length between this time-interval is dependent upon the last few sampling timepoints (usually at least 2 hours between points). In simulation models, the temporal resolution is much higher, typically with an interpolation length of five points per hour. In this PBPK model, elimination half-life was calculated from the last 10% of the predicted datapoints. As a result, small changes in the last 10% of the

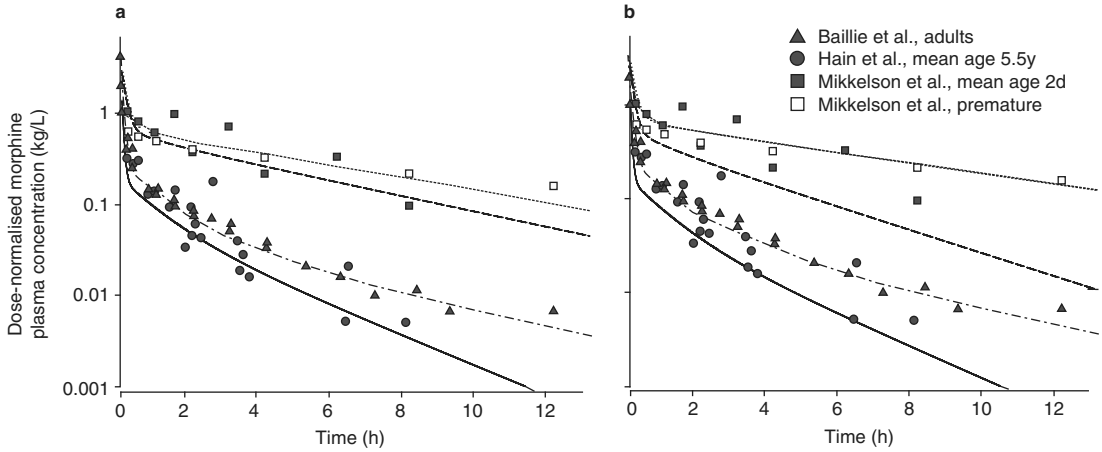

Fig. 5. Predicted dose-normalised plasma concentration-curves (lines) for morphine administration to children. Either the study reported clearance (**a**), or the predicted clearance (**b**) was used as input for the physiologically based pharmacokinetic model. Observed concentration values (symbols) were taken from the literature: mean age 5.5 years from Hain et al.;[93] mean age 2 days and premature from Mikkelsen et al.[92] The adult data from Baillie et al.[78] are presented for reference.

Table IX. Reported and predicted values for the volume of distribution and elimination half-life of paracetamol (acetaminophen), alfentanil, morphine, theophylline and levofloxacin

Study	Drug	Age[a]	Volume of distribution (L/kg)[b]		Elimination half-life (h)[b]	
			reported	predicted	reported	predicted
Hardman and Limbird[23]	Paracetamol	Adults	0.95 (0.12)		2.0 (0.4)	
Allegaert et al.[89]		Premature; <1d	0.61 (0.15) [0.44–1]	0.66	4.6 (2.4) [1.4–11.3]	6.8
Allegaert et al.[89]		Term; <1d	0.64 (0.25) [0.46–1.3]	0.74	2.9 (0.98) [1.6–4.5]	4.7
Autret et al.[90]		<10d	0.7 (0.2)	0.65	3.5 (0.5)	5.5
Autret et al.[90]		10–232d	0.9 (0.1)	0.94	2.1 (0.9)	2.9
Granry et al.[91]		8–14y	0.95 (0.1)	0.90	1.6 (0.09)	2.1
Hardman and Limbird[23]	Alfentanil	Adults	0.8 (0.3)		1.6 (0.2)	
Marlow et al.[99]		25–36wk (30wk)]; <4d PNA[c]	0.50 [0.13–1.0]	0.27	5.4 [1.1–17.3]	6.4
Davis et al.[100]		29.5wk[c,d]	1.0 (0.39)	0.45	8.8 (5.1)	2.8
Killian et al.[101]		36wk (0.98); <3d PNA[c]	0.82 (0.3)	0.45	5.4 (0.8)	3.6
Goresky et al.[97]		2.4–10.8mo	0.55 (0.21) [0.38–0.94]	0.58	1.3 (0.28) [0.83–1.6]	1.2
den Hollander et al.[102]		4–10mo[e]	0.48 (0.12) [0.33–0.64]	0.34	1.2 (0.42) [0.85–2.0]	1.2
Davis et al.[100]		0.75–10y[f]	0.48 (0.19)	0.42	(0.18)	1.1
Roure et al.[24]		0.83–6.5y	1.0 (0.71) [0.33–3.82][g]	1.1[g]	1.1 (0.4) [0.65–2.6]	0.94
Goresky et al.[97]		1–14.7y	0.48 (0.24) [0.24–1.1]	0.45	1.3 (0.52) [0.72–2.3]	1.0
den Hollander et al.[102]		2.5–8y[e]	0.31 (0.08) [0.24–0.42]	0.19	1.0 (0.15) [0.88–1.2]	1.1
Meistelmans et al.[98]		4.5–7.7y	0.16 [0.078–0.37]	0.39	0.67 (0.15) [0.5–0.95]	1.4
Hardman and Limbird[23]	Morphine	Adults	3.3 (0.9)		1.9 (0.5)	
Mikkelsen et al.[92]		25–32wk (28wk); <18d PNA[c]	2.4 [1.6–2.8][g]	2.1[g]	9.3 [4.1–13.9]	6.4
Bhat et al.[103]		28wk (2.0)	1.8 (0.84)	1.4	10.0 (3.7)	8.1
Mikkelsen et al.[92]		1–18d[c]	1.8 [0.63–2.7][g]	1.9[g]	3.7 [1.8–6.7]	3.6
Bhat et al.[103]		1.3d (0.6)[c]	2.9 (2.1)	1.9	6.7 (4.6)	6.8
Olkkola et al.[104]		0.4–5mo[c,d]	1.8 (0.81) [0.84–3.1]	1.6	1.2 (2.4) [0.6–5.8]	1.4
Olkkola et al.[104]		1.2–4.5y[c,d]	2.9 (1.3) [1.4–5.0]	3.4	0.77 (1.0) [0.4–2.4]	1.3

Continued next page

Table IX. Contd

Study	Drug	Age[a]	Volume of distribution (L/kg)[b]		Elimination half-life (h)[b]	
			reported	predicted	reported	predicted
Olkkola et al.[104]		6.0–6.6y[c,d]	3.5 (1.8) [2.1–7.0]	3.5	1.2 (0.43) [0.87–1.8]	1.3
Pokela et al.[105]		0.3–3d	1.2 [0.9–2.4]	1.5	2.5 [1.2–4.9]	2.8
Pokela et al.[105]		11–57d	2.0 [1.0–2.3]	1.6	3.3 [2.7–11.0]	3.0
Pokela et al.[105]		72–151d	3.6 [1.7–5.6]	2.8	2.0 [1.4–3.3]	2.5
Hain et al.[93]		1.4–15.9y	3.6	3.7	1.5	1.8
Gisclon et al.[81]	Theophylline	Adults	0.44 (0.053)		8.2 (1.8)	
Aranda et al.[106]		25–32wk (27wk); 3–15d PNA	0.69 (0.095) [0.43–1.1]	0.45	30.2 (6.5) [14.4–57.7]	27.1
Simons and Simons[107]		3–23mo	0.34 (0.2) [0.16–0.83][g,h]	0.49[h]	4.4 (2.2) [2.2–8.6]	4.8
Loughnan et al.[94]		1–4y	NA	0.46	3.4 (1.1)	4.2
Vichyanond et al.[108]		7–12y	0.44 [0.37–0.66]	0.43	4.1 [2.0–7.0]	4.4
Arnold et al.[95]		8.8–12.6y	0.44 (0.05)	0.43	4.1 (1.4)	5.1
Ellis et al.[96]		6.1–16.8y	0.42 (0.064) [0.27–0.51]	0.43	3.7 (1.1) [1.4–7.9]	4.6
Agbaba et al.[109]		10–16y	NA	0.42	5.2 (0.68) [3.3–9.5]	4.4
Chien et al.[82]	Levofloxacin	Adults	1.3 (0.12)		6.0 (1.0)	
Chien et al.[82]		0.5–2y	1.6 (0.3)	1.5	4.1 (1.3)	5.1
Chien et al.[82]		2–5y	1.5 (0.21)	1.3	4.0 (0.8)	3.6
Chien et al.[82]		5–10y	1.6 (0.44)	1.4	4.8 (0.8)	5.2
Chien et al.[82]		10–12y	1.4 (0.35)	1.3	5.4 (0.8)	6.7
Chien et al.[82]		12–16y	1.6 (0.53)	1.3	6.0 (2.1)	8.2

a Range (mean).

b Values are expressed as mean (SD) [range].

c The lungs of all patients were ventilated.

d Patients were intubated.

e Patients undergoing surgery with extracorporeal circulation.

f Patients undergoing major surgery.

g Volume of distribution calculated as CL/k_e where CL is clearance and k_e is the terminal elimination rate constant.

h Clearance, and thus, volume of distribution, was measured using the concentration in plasma just prior to ceasing the infusion.

NA = not applicable; **PNA** = postnatal age.

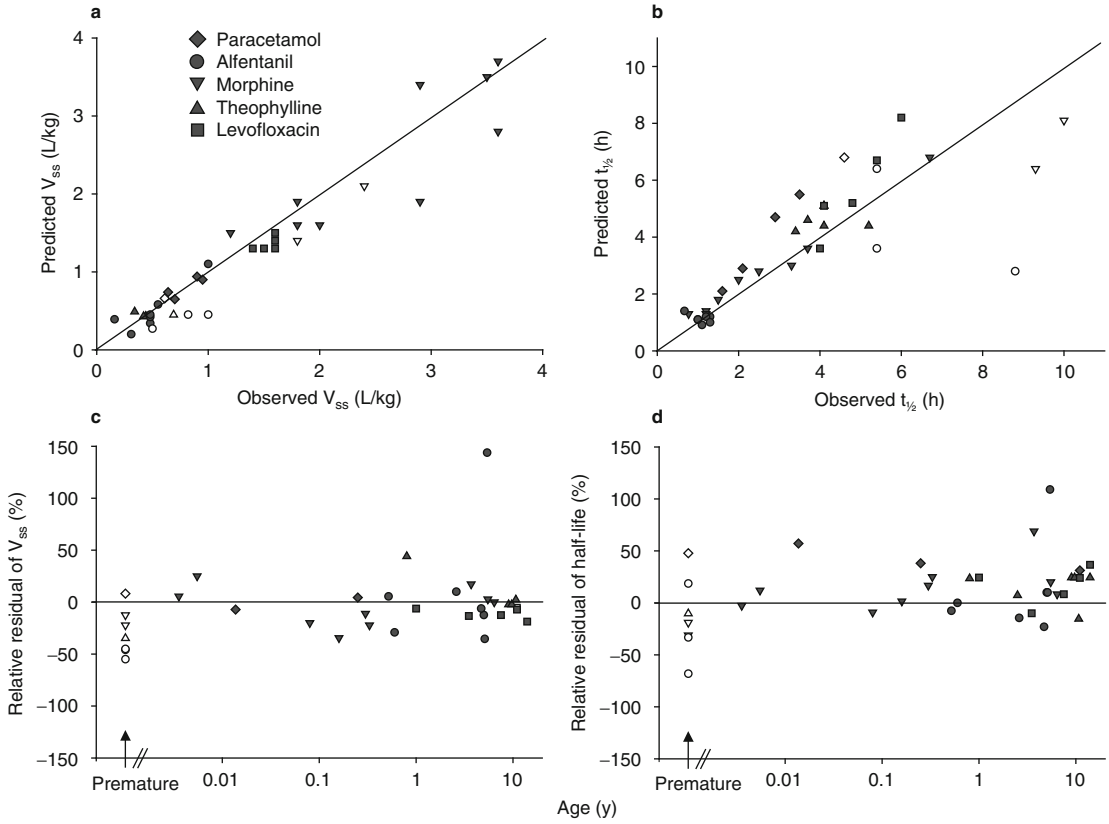

Fig. 6. Observed vs predicted volume of distribution at steady state (V_{ss}) [**a**] and elimination half-life ($t_{½}$) [**b**] data for paediatric studies using paracetamol (acetaminophen), alfentanil, morphine, theophylline and levofloxacin. Open symbols represent data from premature neonates. (**c**) The relative residuals ([predicted value – observed value]/observed value × 100) vs age for the data in (**a**). (**d**) The relative residuals vs age for the data in (**b**). One data point was not presented in (**b**) for visual purposes (premature group administered paracetamol with predicted and observed $t_{½}$ of 30.2 and 27.1 hours, respectively).

datapoints because of distribution (i.e. another compartment, causing increased upwards curvature of the line) can lead to a predicted elimination half-life, which is longer than the experimentally observed elimination half-life. Bjorkman[16] used clearance and volume of distribution to calculate elimination half-life with the knowledge that any over- or under-prediction of these values would lead to erroneous elimination half-lives. We chose the 10% scheme to attempt to circumvent this problem.

In PK-Sim®, as in all PBPK models, clearance is a highly important input parameter. The trends associated with the extent of exposure in children, in relation to adult exposures, are regulated, in a large part, by clearance. In our study, the reported clearances for children were used without regard for their method of generation, although it was obvious, in some cases, that the reported literature value was incorrectly calculated. This was the case for at least two studies.[98,104] In one alfentanil study,[98] this can be readily seen where the predicted curve, using the reported clearance of 4.7 mL/min/kg, was very far from the observed plasma concentration values (see the Meistelmens et al.[98] curve in figure 4a). This study was also the major outlier for volume of distribution in figure 6b. When the predicted clearance value (8.9 mL/min/kg) was used, the predicted curve was very close to the observed values (see figure 4a). A similar plasma concentration-time curve for the same age range (see Goresky et al.[97]

curve in figure 4a), reported a very different, but more reasonable clearance value. In the case of one study using morphine,[104] the reported hepatic *in vivo* clearance was far above the Q_H for the age group tested. Subsequent compartmental modelling by us confirmed that the reported clearance values were unlikely. The input of the predicted clearances in the model produced the correct trend in the positioning of the predicted curve relative to adults in all cases.

Among the paediatric age range premature neonates require special consideration. For this age group, the volumes of distribution and elimination half-lives were generally underpredicted. Our PBPK model was developed for children from term onwards and it is evident from the distribution analysis that term neonate PBPK parameters did not adequately predict these values in premature neonates. However, the plasma concentration-time curves were well represented in some cases (see figures 3–5). This is the likely result of both the large variability in volumes of distribution in this age group and of the PBPK model, not taking into account the greater body water and lower lipid levels observed in premature neonates in relation to term neonates and children.[67] This PBPK model should be used cautiously for the prediction of pharmacokinetics in premature neonates.

In vivo data tend to focus on the older age groups. There were limited *in vivo* data available for these compounds within the first year of life; a time when substantial developmental changes occur. We recommend using PBPK modelling to understand the directional changes in pharmacokinetics that may occur during this timeframe, but urge caution in implementing dosing or regimens changes without careful monitoring procedures in place. Furthermore, paediatric patients commonly have pathological conditions, which themselves can alter their physiology. The anatomical and physiological data used in this model represented those of healthy children; however, the body composition, for example, can be much different in sick children experiencing disease related effects, such as malnutrition. As a next step, it would be desirable to collect information about the physiological and anatomical alterations related to certain pathological conditions to further refine the model; research is currently ongoing for children with cystic fibrosis.

Conclusion

PBPK model use has been recommended for paediatric risk assessment by an expert panel in a workshop forum.[110] Perceived obstacles to PBPK modelling in children included the characterisation of body composition, blood flows, metabolic differences and the general lack of paediatric pharmacokinetic and toxicokinetic data.[110] The current study, in conjunction with Edginton et al.,[14] has addressed the physiological aspects of PBPK modelling in children with evaluation using five drugs having different physiochemical parameters. This study suggests that pharmacokinetic simulation in children can be a useful predictive tool for paediatric clinical trial preparation. Modelling and simulation provide a means for guiding dosing regimens and dosages. Furthermore, approximating blood collection times will increase the efficiency of sampling, aid in pharmacokinetic/pharmacodynamic modelling [8] and ultimately, reduce the number of patients required to participate. The sharp rise in paediatric clinical trials since the initiation of the 1997 Pediatric Exclusivity Provision[2] lends itself well to the investigation of PBPK models for paediatric clinical trial preparation.

Acknowledgements

No specific funding was received for this project. All authors are employed by Bayer Technology Services (BTS) GmbH.

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