ORIGINAL RESEARCH ARTICLE

Extrapolation of Drug Clearance in Children ≤ 2 Years of Age from Empirical Models Using Data from Children (> 2 Years) and Adults

Iftekhar Mahmood[1,2]

Abstract

Background The application of modeling and simulation approaches in clinical pharmacology studies has gained momentum over the last 20 years.

Objectives The objective of this study was to develop six empirical models from clearance data obtained from children aged > 2 years and adults to evaluate the suitability of the models to predict drug clearance in children aged ≤ 2 years (preterm, term, and infants).

Methods Ten drugs were included in this study and administered intravenously: alfentanil, amikacin, busulfan, cefetamet, meperidine, oxycodone, propofol, sufentanil, theophylline, and tobramycin. These drugs were selected according to the availability of individual subjects' weight, age, and clearance data (concentration–time data for these drugs were not available to the author). The chosen drugs are eliminated by extensive metabolism by either the renal route or both the renal and hepatic routes. The six empirical models were (1) age and body weight-dependent sigmoidal maximum possible effect (E_{max}) maturation model, (2) body weight-dependent sigmoidal E_{max} model, (3) uridine 5′-diphospho [body weight-dependent allometric exponent model (BDE)], (4) age-dependent allometric exponent model (ADE), (5) a semi-physiological model, and (6) an allometric model developed from children aged > 2 years to adults. The model-predicted clearance values were compared with observed clearance values in an individual child. In this analysis, a prediction error of ≤ 50% for mean or individual clearance values was considered acceptable.

Results Across all age groups and the ten drugs, data for 282 children were compared between observed and model-predicted clearance values. The validation data consisted of 33 observations (sum of different age groups for ten drugs). Only three of the six models (body weight-dependent sigmoidal E_{max} model, ADE, and semi-physiological model) provided reasonably accurate predictions of clearance (> 80% observation with ≤ 50% prediction error) in children aged ≤ 2 years. In most instances, individual predicted clearance values were erratic (as indicated by % error) and were not in agreement with the observed clearance values.

Conclusions The study indicated that simple empirical models can provide more accurate results than complex empirical models.

✉ Iftekhar Mahmood
    Iftekharmahmood@aol.com

1 Office of Tissue and Advanced Therapies (OTAT), Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002, USA

2 Present Address: Mahmood Clinical Pharmacology, Consultancy, LLC, 1709, Piccard Dr, Rockville, MD 20850, USA

1 Introduction

Children can require medication for the cure or management of diseases. Neonates, infants, children, adolescents, and adults differ not only in body weight but also in physiology and biochemistry. The pharmacokinetic (PK) differences across the wide age range are mainly due to differences in drug metabolism and renal function [1].

In the last 20 years, modeling and simulation for the prediction of both PK parameters and dose in pediatric populations has gained momentum [2]. The most commonly used methods for the prediction of drug clearance and dose include allometric models, population pharmacokinetic (POPPK) models and physiologically based pharmacokinetic (PBPK) models [2].

Key Points

In some situations, concentration–time data may not be available to characterize the pharmacokinetics of a drug in children aged ≤ 2 years, especially in neonates and infants.

This study evaluated whether empirical models developed from children aged > 2 years to adults can be used to predict clearance in children aged ≤ 2 years.

The results indicated that only three of six empirical models (body weight-dependent sigmoidal E_{max} model, ADE, and semi-physiological model) were useful (prediction error ≤ 50%) for the prediction of drug clearance in children aged ≤ 2 years.

The study indicated that simple empirical models can provide more accurate results than complex models. Caution is needed when using these empirical models for extrapolation purposes.

The ideal method of determining PK parameters in children for a given age group is to conduct a PK study in that age group. The important PK parameters are clearance, volume of distribution, and half-life [3], with clearance being the most important parameter as it has a critical role in determining a safe and effective dose [2]. Clearance can also be used for the first-in-children dose selection (clinical trial) [2]. Therefore, during drug development, it is important to predict PK parameters (especially clearance) in children of different age groups to designate a first-in-children dose [2]. Adult data can be helpful in deciding a first-in-children dose to initiate a clinical trial of new drugs through modeling.

It is difficult and sometimes impossible to conduct a PK study in preterm and term neonates, infants, and toddlers. As such, PK parameters are often predicted from adult data or a combination of adult–children data, especially in young children. PK data from children aged > 2 years may sometimes be available, and such a combination of data can be used to develop a model that may be suitable to predict drug clearance in children aged ≤ 2 years.

The objective of this study was to develop six empirical models from clearance data obtained from children aged > 2 years and adults to evaluate the suitability of the models to predict the drug clearance in children aged ≤ 2 years with reasonable accuracy (a prediction error of ≤ 50% on mean observed clearance). The following six models were developed and evaluated for their predictive performance for clearance of studied drugs. These six models are widely used for the extrapolation (from adults to neonates) of drug clearance. It should be noted that models 1–3 require data from neonates to adults to develop an empirical model, so

theoretically may not be suitable for extrapolation purposes. Since the theories must reconcile with the observations, the author evaluated these three models to confirm whether the theoretical notion of these three models is correct.

- Age and body weight-dependent sigmoidal maximum possible effect (E_{max}) maturation model.
- Body weight-dependent sigmoidal E_{max} model.
- Body weight-dependent allometric exponent model (BDE).
- Age-dependent allometric exponent model (ADE).
- A semi-physiological model.
- A simple allometric model developed from children aged > 2 years to adults.

2 Methods

Clearance values for ten drugs from neonates to adults for ten drugs administered intravenously were obtained from the literature [see the reference list in the electronic supplementary material (ESM)]: alfentanil, amikacin, busulfan, cefetamet, meperidine, oxycodone, propofol, sufentanil, theophylline, and tobramycin. These drugs were selected according to the availability of individual subjects' weight, age, and clearance data (concentration–time data for these drugs were not available to the author). The chosen drugs are eliminated by extensive metabolism, either exclusively via the renal route or via both the renal and the hepatic route. Clearance values for the studied drugs were estimated by either compartmental or noncompartmental analysis in the original studies by the respective authors using extensive blood sampling.

Clearance data for a given drug were pooled from several studies reported in the literature across different observations and divided into two groups: data for model development (aged > 2 years to adults) and data for model evaluation (aged ≤ 2 years).

Drug clearance in an individual subject was predicted using the model parameters and compared with the observed clearance value in that individual. Mean observed and predicted clearance values were calculated from the individual observed and predicted clearance values and compared. The following methods were used to develop the different empirical models.

2.1 Model 1: Age- and Body Weight-Dependent Sigmoidal Maximum Possible Effect (E_{max}) Maturation Model

Equation (1) describes a maturation model [4] that incorporates both body weight and age.

$$CL = CL_{std} \times \left(\frac{BW}{70}\right)^{0.75} \times \frac{(PMA)^{HillCL}}{(PMA)^{HillCL} + (CL_{mat50})^{HillCL}}, \tag{1}$$

where CL_{std} is the population estimate for drug clearance, BW is the individual body weight, and 0.75 is a theoretical allometric exponent on body weight. PMA is postmenstrual age in weeks, CL_{mat50} is the PMA at which clearance was 50% of the mature value, and $Hill_{CL}$ is an exponent that describes the steepness of the maturation function.

Individual reported clearance values from children aged > 2 years and adults were normalized to $(BW/70 kg)^{0.75}$. The parameter estimates of the right-hand side of Eq. (1) (CL_{std}, CL_{mat50}, and $Hill_{CL}$) were obtained by fitting the body weight normalized clearance to the corresponding PMA. Data were analyzed using Phoenix [5] for all equations.

2.2 Model 2: Body Weight-Dependent Sigmoidal E_{max} Model

A recent study [6] indicated that a sigmoidal E_{max} model can be used to describe the body weight versus clearance data across the observations. This study evaluated the predictive performance of a sigmoidal E_{max} model for ten drugs. The model requires only body weight and clearance data (age is not a covariate in this model). Equation (2) describes the sigmoidal E_{max} model.

$$CL = CL_{std} \times \frac{(BW)^{HillCL}}{(BW)^{HillCL} + (CL_{mat50})^{HillCL}}, \tag{2}$$

where CL_{mat50} is the body weight at which clearance was 50% of an adult subject (see Sect. 2.1 for definitions of all other terms in this equation).

2.3 Model 3: Body Weight-Dependent Allometric Exponent Model (BDE)

The model [7] requires only body weight and clearance data (age is not a covariate in this model). The relationship between individual body weight and individual clearance values of different age groups are described by Eq. (3).

$$CL = coefficient \times \left(\frac{BW}{70}\right)^{L \times BW^{(-m)}}, \tag{3}$$

where the expression $L \times BW^{-m}$ defines the body weight-dependent exponent for clearance. The coefficient and the exponents L and m were estimated using NONMEM VII 3.0 (ICON Development Solutions, Hanover, MD, USA).

2.4 Model 4: Age-Dependent Exponent Model (ADE)

In this method [8], different exponents were used for different age groups, and clearance was predicted in a given age group according to Eq. (4).

$$CL = Adult\ CL \times \left(W_C/W/70_A\right)^b, \tag{4}$$

where the "adult clearance" is the mean adult clearance of a given drug obtained from the literature, W_C is the weight of a child, and $W/70_A$ is the weight of an adult standardized to 70 kg.

Exponent 'b' in Eq. (4) is age dependent. The age-dependent exponents, as described previously [8], were 1.2 for preterm neonates (0–3 months), 1.1 for term neonates (0–3 months), 1.0 for > 3 months–2 years, 0.9 for > 2–5 years, and 0.75 for > 5 years. Since this study predicted drug clearance in children aged ≤ 2 years, the ADE exponents used were 1.2 for preterm and term neonates, 1.0 for term neonates, and 0.9 for > 3 months–2 years. The exponents in the ADE model were selected based on previous experience, observation, and data analysis [8].

2.5 Model 5: Semi-Physiological Model

The first step in the development of this model [8] was to predict the weight and blood flow for the liver and kidneys in a given child as a function of body weight. Allometric models for these physiological parameters were developed using data from neonates to adults [9]. The following allometric equations were obtained for these parameters.

$$Liver\ weight\ in\ a\ child = 0.048 \times (body\ weight)^{0.847}$$
$$(r^2 = 0.990), \tag{5}$$

$$Kidney\ weight\ in\ a\ child = 0.010 \times (body\ weight)^{0.807}$$
$$(r^2 = 0.987), \tag{6}$$

where both body and organ weights are in kilograms.

$$Hepatic\ blood\ flow\ in\ a\ child = 0.088 \times (body\ weight)^{0.706}$$
$$(r^2 = 0.990), \tag{7}$$

$$Kidney\ blood\ flow\ in\ a\ child = 0.012 \times (body\ weight)^{1.121}$$
$$(r^2 = 0.983), \tag{8}$$

where blood flow is in liters/minute and body and organ weights are in kilograms.

From Eqs. (5)–(8), organ weights and blood flow rates were determined in a child and then divided by adult values. The sum of all four physiological parameters was then used

to predict drug clearance in that child according to the following equation:

$$\text{CL in a child} = \text{adult CL} \times \text{sum of the parameters}$$
$$\times (\text{weight of the child}/70)^{0.75}. \qquad (9)$$

where CL is clearance.

2.6 Model 6: Allometric Model Developed From Children Aged > 2 years to adults

In this model, the exponent of allometry for a given drug was determined from the clearance versus body weight values, and the clearance of a drug was predicted from Eq. (10)

$$\text{CL} = \text{coefficient} \times \left(W_C/W70_A \right)^b, \qquad (10)$$

where W_C is the weight of a child and $W/70_A$ is the weight of an adult standardized to 70 kg, and "b" is the exponent of allometry determined from clearance versus body weight data.

2.7 Statistical Analysis

Percent error between the observed and predicted values was calculated according to the following equation:

$$\%\text{error} = \frac{(\text{Predicted} - \text{observed}) \times 100}{\text{observed}}. \qquad (11)$$

In this analysis, an arbitrarily selected prediction error of $\leq 50\%$ for mean clearance values was considered acceptable, but a more rigid acceptance criterion such as $\leq 30\%$ was also evaluated.

3 Results

Table S1 in the ESM provides a description of the sample size and age range for model development for the ten drugs and shows the adult clearance values used in model 4 (ADE) and model 5 (semi-physiological model). Table S2 in the ESM shows the predicted and observed clearance values of the ten drugs by different models for children aged ≤ 2 years. Using the models, the clearances of the ten drugs were predicted in an individual child, but the results are presented as mean clearance in a given age group for a given drug. In most instances, the individual predicted clearance values were erratic (as indicated by % error) and were not in agreement with the observed clearance values. In this analysis, a prediction error $\leq 50\%$ for mean or individual clearance values was considered acceptable. The study results for each of the models are summarized in the following subsections.

3.1 Model 1: Age- and Body Weight-Dependent Sigmoidal E_{max} Maturation Model

Table S3 in the ESM shows the estimated maturation model parameters (CL_{std}, PMA_{50}, and $Hill_{CL}$) for the ten drugs along with parameter precision [%coefficient of variation (%CV)]. The %CV was < 20% for CL_{std} for all ten drugs, indicating a good estimate of this parameter (the predicted CL_{std} values reconciled very well with the reported clearance values in adults). The %CV for CL_{mat50} and $Hill_{CL}$ were substantial, reaching a percentage of several thousands, indicating the lack of precision in the parameter estimate. This finding is not surprising as the development of maturation models requires data from neonates to adults. Although this model can be rejected based on the internal model evaluation criteria described, the author further evaluated it with external data to characterize its predictive performance. Table 1 summarizes the mean predicted and observed clearance values in different age groups for the ten drugs from the maturation model. The mean predicted clearance values were not in good agreement with the observed mean clearance values.

Of 33 observations (total number of children in different age groups for the ten drugs), the error in mean predicted clearance was $\leq 50\%$ and $\leq 30\%$ for 17 (52%) and 9 (27%) observations, respectively (Table 1). There were 11 (33%) and 16 (48%) observations for mean clearance with > 100% and > 50%, respectively (Table 1).

Drug clearance was further stratified according to age. Nine observations were available for preterm neonates, and the prediction error was > 100% for eight of them (Table 2). Of 11 observations in term neonates, the prediction error was $\leq 50\%$ and > 50% for six (55%) and five (45%), respectively (Table 3).

In most cases, the prediction of drug clearance in individual subjects was inaccurate. The individual prediction error was $\leq 30\%$ for 35% of individual subjects, $\leq 50\%$ for 54% of subjects, and $\geq 50\%$ for 46% of subjects ($n = 282$) (Table 4).

Overall, the study results suggest that a valid maturation model cannot be developed using data from children aged > 2 years and adults. Therefore, a maturation model cannot be used for the prediction of drug clearance in children aged ≤ 2 years, especially in preterm and term neonates.

3.2 Model 2: Body Weight-Dependent Sigmoidal E_{max} Model

Table S3 in the ESM shows the estimated maturation model parameters (CL_{std}, PMA_{50}, and $Hill_{CL}$) for the ten drugs, along with parameter precision (%CV). The %CV for CL_{std} ranged from 10 to 79% for all ten drugs. For four drugs, %CV for CL_{std} was > 50%. The predicted CL_{std} values were slightly higher than the reported clearance values in adults. The %CV for CL_{mat50} and $Hill_{CL}$ was not as high as seen with

Table 1 Summary of the results by different methods ($n=33$)

Error (%)	Model I	Model II	Model III	Model IV	Model V	Model VI
≤ 50	17 (52)	27 (82)	15 (54)	31 (94)	30 (91)	10 (30)
≤ 30	9 (27)	20 (61)	11 (39)	21 (64)	20 (61)	7 (21)
> 50	16 (48)	6 (18)	12 (43)	2 (6)	3 (9)	23 (70)
> 100	11 (33)	3 (9)	5 (18)	0 (0)	0 (0)	17 (52)

Numbers in parentheses are % of the total number of observations ($n=33$); method III, $n=27$

Model I = sigmoidal maturation (age and body weight); model II = sigmoidal (weight vs. clearance); model III = body weight-dependent allometric exponent model; model IV = age-dependent allometric exponent model; model V = semi-physiological; model VI = allometric model

Table 2 Summary of the results by different methods (preterm; $n=9$)

Error (%)	Model I	Model II	Model III	Model IV	Model V	Model VI
≤ 50	0 (0)	8 (89)	1 (14)	9 (100)	9 (100)	0 (0)
≤ 30	0 (0)	7 (78)	1 (14)	7 (78)	5 (56)	0 (0)
> 50	9 (100)	1 (11)	6 (86)	0 (0)	0 (0)	9 (100)
> 100	8 (89)	1 (11)	3 (43)	0 (0)	0 (0)	9 (100)

Numbers in parentheses are % of the total number of observations ($n=9$); method III, $n=7$

Table 3 Summary of the results by different methods (term; $n=11$)

Error (%)	Model I	Model II	Model III	Model IV	Model V	Model VI
≤ 50	6 (55)	9 (82)	5 (56)	11 (100)	10 (91)	3 (27)
≤ 30	3 (27)	4 (36)	4 (44)	10 (91)	9 (82)	2 (18)
> 50	5 (45)	2 (18)	4 (44)	0 (0)	1 (9)	8 (73)
> 100	2 (18)	1(9)	1 (11)	0 (0)	0 (0)	5 (45)

Numbers in parentheses are % of the total number of observations ($n=11$); method III, $n=9$

Table 4 Percent of individual subjects within a category of % error

Error (%)	Model I	Model II	Model III	Model IV	Model V	Model VI
≤ 30	35	43	30	41	45	22
≤ 50	54	68	53	72	71	37
> 50	46	32	47	28	29	63

$n=282$ for models I, II, IV–VI, and 203 for model III

the sigmoidal maturation model. CV > 100% on CL_{mat50} and $Hill_{CL}$ was 3 and 0, respectively. Overall, the estimate of CL_{mat50} and $Hill_{CL}$ was far more accurate (based on %CV) for model 2 than for model 1.

The mean predicted and observed clearance values in different age groups for the ten drugs from model 2 are summarized in Table 1. The mean predicted clearance values were in good agreement with the observed mean clearance values.

Of 33 observations, the error in mean predicted clearance was ≤ 50% and ≤ 30% for 27 (82%) and 20 (61%) observations, respectively (Table 1). There were three (9%) and six (18%) observations for mean clearance, with > 100% and > 50%, respectively (Table 1).

Nine observations were available for preterm neonates, and the prediction error of ≤ 50% and ≤ 30% was noted for eight (89%) and seven (78%) observations, respectively (Table 2). Of 11 observations in term neonates, the prediction error was ≤ 50% and > 50% for nine (82%) and two (18%), respectively (Table 3).

In most instances, the prediction of drug clearance in individual subjects was inaccurate. The individual prediction error was ≤ 30% for 43% of individual subjects, ≤ 50% for 68% of subjects, and ≥ 50% for 32% of subjects ($n=282$) (Table 4).

Overall, the study results suggested that model 2 developed from children aged > 2 years to adults predicted drug clearances in children aged ≤ 2 years reasonably well.

3.3 Model 3: BDE

Table S4 in the ESM shows the estimated BDE model parameters (coefficients and exponents L and M) and parameter precision (%CV) for eight drugs. The BDE model could not be fitted (the program did not converge) to propofol and tobramycin. The %relative standard error (%RSE) was < 10% for coefficients, and the projected clearance values in adults were close to the observed clearance values. The %RSE for exponent L was < 100% for six of eight drugs. On the other hand, %RSE was > 100% for six of eight drugs for exponent m, indicating the lack of precision in the estimation of this exponent. This finding is not surprising as the development of the BDE model required data from neonates to adults. Table S4 in the ESM shows the coefficients and the exponents of the BDE model.

Based on internal model evaluation criteria, this model can be rejected, but the author further characterized the extrapolation ability of the BDE model using external data. Table S4 in the ESM summarizes the mean predicted and observed clearance values in different age groups for eight drugs from the BDE model. The mean predicted clearance values were not in good agreement with the observed mean clearance values.

Of 27 observations, the error in mean predicted clearance was ≤ 50% for 15 (54%) and ≤ 30% for 11 (39%) observations (Table 1). There were five (18%) and 12 (43%) observations for mean clearance, with > 100% and > 50%, respectively (Table 1).

There were seven observations for preterm neonates, and prediction errors of ≤ 50% and ≤ 30% were noted for one (14%) observation each (Table 2). Of nine observations in term neonates, the prediction error was ≤ 50% for five (56%) and > 50% for four (44%) (Table 3).

In most cases, the prediction of drug clearance in individual subjects was inaccurate. The individual prediction error was ≤ 30% for 30% of individual subjects, ≤ 50% for 53% of subjects, and ≥ 50% for 47% of subjects ($n = 203$) (Table 4).

Overall, the study results suggest that a valid BDE model cannot be developed using data from children aged > 2 years and adults. Therefore, the BDE model cannot be used to predict drug clearances in children aged ≤ 2 years, especially in preterm and term neonates.

3.4 Model 4: ADE

Unlike models 1–3, ADE uses only adult data for the prediction of drug clearance in children of different age groups using different exponents for different age groups as described in Sect. 2. Table S1 in the ESM shows the adult clearance values used in the ADE model, and Table S2 summarizes the mean predicted and observed clearance values in different observations for the ten drugs from the ADE model. The mean predicted clearance values were in good agreement with the observed mean clearance values.

Of 33 observations, the error in mean predicted clearance was ≤ 50% for 31 (94%) observations and ≤ 30% for 21 (64%) observations (Table 1). Two (6%) observations had a prediction error > 50% (Table 1), with the highest being 65%.

Nine observations were available for preterm neonates, and the prediction error was ≤ 50% for nine (100%) observations and ≤ 30% for seven (78%) observations (Table 2). Of 11 observations in term neonates, the prediction error was ≤ 50% for 11 (100%); the prediction error was not > 50% for any observations (Table 3).

In most instances, the prediction of drug clearance in individual subjects was inaccurate. The individual prediction error was ≤ 30% for 41% of subjects, ≤ 50% for 72% of subjects, and ≥ 50% for 28% of subjects ($n = 282$) (Table 4).

Overall, the study results suggest that the ADE developed from adult clearance values predicted drug clearances in children aged ≤ 2 years very well. In particular, the prediction of clearance in preterm and term neonates was excellent.

3.5 Model 5: Semi-Physiological Model

Unlike a whole-body PBPK, which incorporates almost all body organs and many physiological entities, model 5 uses only four physiological parameters as described in Sect. 2. In this model, besides four physiological parameters, adult clearance data and a theoretical exponent 0.75 on body weight were also used.

Table 2 summarizes the mean predicted and observed clearance values in different observations for the ten drugs from model 5. The mean predicted clearance values were in good agreement with the observed mean clearance values.

Of 33 observations, the error in mean predicted clearance was ≤ 50% for 30 (91%) and ≤ 30% for 20 (61%) observations (Table 1). Three (9%) observations had a prediction error > 50% (Table 3), with the highest being 58%.

Nine observations were available for preterm neonates, and the prediction error was ≤ 50% for nine (100%) and ≤ 30% for five (56%) observations (Table 2). Of 11 observations in term neonates, the prediction error was ≤ 50% for ten (91%) and ≤ 30% for nine (82%) observations (Table 3). Only one age group had a > 50% prediction error (56%).

In most cases, the prediction of drug clearance in individual subjects was inaccurate. The individual prediction error was ≤ 30% for 45%, ≤ 50% for 71%, and ≥ 50% for 29% of individual subjects ($n = 282$) (Table 4).

Overall, the study results suggest that model 5, developed from adult clearance values, predicted drug clearances in children aged ≤ 2 years very well. In particular, the prediction of clearance in preterm and term neonates was very good.

3.6 Model 6: Allometric Model Developed From Children Aged > 2 Years and Adults

This model was developed using the clearance and body weights from children aged > 2 years to adults, as shown in Eq. (10). Table S5 in the ESM shows the coefficients and the exponents of the allometric model. A correlation (r^2) of > 0.65 between body weight and clearance was noted for six of ten drugs.

Table 2 summarizes the mean predicted and observed clearance values in different observations for the ten drugs from model 6. The mean predicted clearance values were not in good agreement with the observed mean clearance values.

Of 33 observations, the error in mean predicted clearance was ≤ 50% for ten (30%) and ≤ 30% for seven (21%) observations (Table 1). There were 17 (52%) and 23 (70%) observations for mean clearance with > 100% and > 50%, respectively (Table 1).

Nine observations were available for preterm neonates, and the prediction error was > 100% for all nine preterm neonates (Table 2). Of 11 observations in term neonates, the prediction error was ≤ 50% for three (27%) and > 50% for eight (73%) (Table 3).

In most instances, the prediction of drug clearance in individual subjects was inaccurate. The individual prediction error was ≤ 30% for 22% of subjects, ≤ 50% for 37%, and ≥ 50% for 63% of subjects ($n = 282$) (Table 4).

Overall, the study results suggest that the allometric model developed from children aged > 2 years to adults has very poor prediction of drug clearance in children aged ≤ 2 years.

4 Discussion

The application of modeling and simulation approaches in clinical pharmacology studies has gained momentum over the last 20 years. Models such as the sigmoidal E_{max} maturation model and BDE can be used to estimate drug clearance when the data from neonates to adults are available. In this study, six empirical models were used to evaluate the predictive performance of these models, developed from children (aged > 2 years) to adults to predict clearance in children aged ≤ 2 years.

The age- and body weight-dependent sigmoidal E_{max} maturation model [4] is advocated as a model for the estimation of PK parameters across a wide age range. Mahmood et al.

[10] previously used six drugs and developed sigmoidal E_{max} maturation models using data from neonates to adults. The predictive power of the model was assessed using external data (data not included in the model) in children aged ≤ 5 years. The authors noted that the sigmoidal E_{max} maturation model provided a reasonably good prediction of mean clearance of drugs in children aged ≤ 5 years. The results were not surprising since the model included data from the preterm neonates to adults.

Maturation is a physiological process, but maturation models are neither physiological nor have a strong scientific basis, mainly because the model uses a fixed theoretical exponent of 0.75. The sigmoidal parameter values (CL$_{max}$, CL$_{mat50}$, and Hill$_{CL}$) of a maturation model are data dependent and will vary based on sample size, age, and weight range and are not physiologically relevant. The assumption that the exponent 0.75 on body weight and the sigmoidal function on age are the most suitable or optimal approach to describe a maturation model is incorrect [10, 11]. It should be recognized that the exponents of allometry vary widely and are data dependent, and no scientific basis exists for using a fixed exponent across all age groups [7, 8, 10]. Furthermore, the sigmoidal maturation model has created an incorrect impression among modelers that both age and body weight are required to predict or estimate clearance across age. The BDE, ADE, and semi-physiological models belie this notion (in this study). The shortcomings of the maturation model have been discussed in detail previously [11, 12].

The BDE model provides strong evidence that neither age nor weight are needed to estimate drug clearance across age groups [8–13]. Body weight alone is sufficient to predict drug clearance across age groups.

Simple allometric models (body weight vs. clearance) can be used to predict clearance in pediatrics from clearance data obtained from adults. This method does occasionally offer a reasonable prediction of mean drug clearance in children aged ≤ 5 years from adult data, but this study and others [9, 14, 15] found most predictions of mean drug clearance to be erratic with substantial prediction error, especially in children aged ≤ 2 years.

Given that the allometric exponents varied widely, and a single exponent cannot describe the clearance versus body weight data across all age groups, Mahmood [8] introduced the concept of ADE. This model has provided fairly accurate prediction of drug clearance across the age groups, including preterm and term neonates [16–20].

Liver and kidneys are the two most important organs for elimination of drugs from the body. Mahmood [8] developed an allometric model based on kidney and liver weights and blood flow to predict drug clearances in children from preterm neonates to ≤ 2 years of age. This simple physiological model provided fairly accurate prediction of drug clearances. In this and another study [8], the results of this

semi-physiological model were comparable with those from the ADE model.

Besides empirical models, PBPK models are also used to predict drug clearance in children. PBPK modeling requires extensive data (physicochemical properties of drugs, organs, or tissues; blood flow rates, enzymatic activity, etc.). In PBPK modeling, physiological, physicochemical, and biochemical processes are mathematically described. This method of analysis is generally called the "whole-body" PBPK model [21–23]. The realization that not every organ, tissue, or physiological parameter was required to describe concentration–time data in a PBPK model led to the development of "minimal" or "lumped" PBPK models [24, 25]. In short, PBPK models require enormous amounts of potentially unnecessary physiologically based data.

Mahmood et al. [17] developed a semi-physiological model to predict the drug clearance of nine glucuronidated drugs in children aged < 3 months. The model used liver weight and blood flow and uridine 5′-diphospho-glucuronosyltransferase activities and was compared with the whole-body physiological model. Comparative results for mean and individual clearance was obtained by the two models. A previous study [8] and the current study indicate that a semi-physiological model as proposed by Mahmood [8, 17] can provide the same results as a whole-body physiological model.

Among the six empirical models evaluated in this study, the worst was the allometric model (model 6), which had substantial prediction error. The next worst model was the age- and body weight-dependent sigmoidal $E_{\max}$ maturation model (model 1). The model's predictive power for clearance in preterm and term neonates was poor but improved as the age of the children increased. Overall, this model predicted drug clearance in children aged ≤ 2 years only for 52% ($n = 33$) of observations. The BDE model's predictive power was as poor as the sigmoidal $E_{\max}$ maturation model.

The best model was the ADE model, as it predicted drug clearance in children aged ≤ 2 years for 94% of observations. Both in preterm and in term neonates, the ADE model's predictive power for clearance in preterm and term neonates was excellent (prediction error ≤ 50% in all 20 observations). The predictive power for drug clearance by the semi-physiological model was as good as the ADE model.

The study results indicated that three empirical models (sigmoidal $E_{\max}$ maturation model, BDE model, and the allometric model) predicted drug clearance poorly in children aged ≤ 2 years. The estimated sigmoidal parameters of maturation model (PMA$_{50}$ and Hill$_{CL}$) appeared to be unreliable since the %RSE for these two parameters were substantially high, reaching to several thousand percent and indicating the lack of precision in the parameter estimates (Table S1). This is not surprising because the sigmoidal maturation model requires data from neonates to adults to maintain the

sigmoidal shape of the PMA versus normalized clearance. Lack of this sigmoidal part of the PMA versus normalized clearance curve produced erratic parameters, which resulted in poor prediction of clearance in children aged ≤ 2 years. van Dijkman et al. [26] also recently noted that the prediction of lamotrigine clearance in children aged < 2 years with the sigmoidal maturation model was poor.

A similar observation was noted with the BDE model. Lack of data from younger children did not provide accurate allometric exponents that could be used to predict drug clearance in children aged ≤ 2 years.

The allometric model was the worst of the six models evaluated in this study, with predicted clearance values substantially higher than observed clearance values.

The two best models were the ADE and semi-physiological models. Both models were comparable in their predictive power. The prediction error in clearance was ≤ 50% for 94% and 91% of observations by the ADE and semi-physiological model, respectively. Both models provided excellent prediction of clearance in preterm and term neonates (prediction error ≤ 50% in > 90% of observations). It should be noted that both the ADE and the semi-physiological model require only adult data.

Besides the ADE and semi-physiological models, the predictive power of model 2 (body weight-dependent sigmoidal $E_{\max}$ model) also provided acceptable results. Model 2 was far superior in its predictive performance to model 1 and model 3, which require neonatal data for an acceptable prediction of drug clearance in infants. This may be because model 2 is a much simpler model. It only needs body weight, whereas model 1 requires age and uses a theoretical exponent of 0.75, leading to inaccurate predictions in infants. For the BDE model, a lack of neonatal data did not provide the exponents required to predict drug clearance in infants.

The current study indicates the inability of the widely used empirical models to predict drug clearance in children aged ≤ 2 years, particularly in neonates. Over the years, it has been assumed that these models can be used to predict drug clearance in these children and subsequent projection of dose if clinical trials cannot be conducted in younger children. This assumption was made without appropriate model validation. In most cases, the models are internally validated. Internal validation based on statistics does not necessarily indicate a model's accuracy for extrapolation from one age group to another. The selection of an empirical model based on statistical criteria may not lead to an accurate or acceptable model from a practical perspective. Cella et al. [27], Santen et al. [28], and Bonate et al. [29] found that, despite statistical validation, a POPPK model may not predict PK parameters in a new population.

In this study, neither a whole-body nor a lumped PBPK model was used to compare the clearance of studied drugs with other empirical models. Recently, Mahmood and

Tegenge [16] noted that the PBPK model was comparable with the ADE model for the prediction of drug clearance in children aged < 2 years. Two other studies [30, 31] reached the same conclusions.

Given the statement of the renowned statistician George Box [32] that, "essentially all models are wrong but some are useful," it should be recognized that all empirical PK models are at best an approximation of the mean PK parameters and should be used for exploratory purposes and not for confirmatory decision making because the predictive power of these models remains uncertain and erratic. Box [32] further stated that, "Since all models are wrong the scientist cannot obtain a 'correct' one by excessive elaboration. On the contrary following William of Occam he should seek an economical description of natural phenomena. Just as the ability to devise simple but evocative models is the signature of the great scientist so overelaboration and overparameterization is often the mark of mediocrity."

5 Conclusions

Several mathematical models can be used to estimate PK parameters, but caution is required in using these models for extrapolation purposes. Complex models do not necessarily provide accurate or desirable results. On the other hand, the two simple models, namely the ADE and the semi-physiological models, provided comparatively accurate and desirable results.

In an era of "fit for purpose," the search and efforts should be focused on simple models rather than on complex and unnecessary elaborative models that provide no practical advantage over simple models.

Compliance with Ethical Standards

Conflicts of interest Iftekhar Mahmood has no conflicts of interest that are directly relevant to the content of this article. Current position: Founder and CEO of Mahmood Clinical Pharmacology Consultancy, LLC, Rockville, MD, USA.

References

1. Kearns GL, Abdel-Rahman SM, Alander SW, et al. Developmental pharmacology: drug disposition, action, and therapy in infants and children. N Engl J Med. 2003;349:1157–67.
2. Mahmood I. Dosing in children: a critical review of the pharmacokinetic allometric scaling and modelling approaches in paediatric drug development and clinical settings. Clin Pharmacokinet. 2014;53:327–46.
3. Gibaldi M, Perrier D. Pharmacokinetics. 2nd ed. New York: Marcel Dekker; 1982.
4. Anand KJ, Anderson BJ, Holford NH, NEOPAIN Trial Investigators Group, et al. Morphine pharmacokinetics and pharmacodynamics in preterm and term neonates: secondary results from the NEOPAIN trial. Br J Anaesth. 2008;101:680–9.
5. Phoenix WinNonlin 8. Certara USA, Inc., Princeton.
6. Ziesenitz VC, Vaughns JD, Koch G, Mikus G, van den Anker JN. Pharmacokinetics of fentanyl and its derivatives in children: a comprehensive review. Clin Pharmacokinet. 2018;57:125–49.
7. Wang C, Allegaert K, Peeters MY, et al. The allometric exponent for scaling clearance varies with age: a study on seven propofol datasets ranging from preterm neonates to adults. Br J Clin Pharmacol. 2014;77:149–59.
8. Mahmood I. Prediction of drug clearance in premature and mature neonates, infants, and children ≤ 2 years of age: a comparison of the predictive performance of 4 allometric models. J Clin Pharmacol. 2016;56:733–9.
9. Björkman S. Prediction of drug disposition in infants and children by means of physiologically based pharmacokinetic (PBPK) modelling: theophylline and midazolam as model drugs. Br J Clin Pharmacol. 2005;59:691–704.
10. Mahmood I, Staschen CM, Goteti K. Prediction of drug clearance in children: an evaluation of the predictive performance of several models. AAPS J. 2014;16:1334–43.
11. Mahmood I. Evaluation of a morphine maturation model for the prediction of morphine clearance in children: how accurate is the predictive performance of the model? Br J Clin Pharmacol. 2011;71:88–94.
12. Mahmood I. Response to the comments of Professors Anderson & Holford. Br J Clin Pharmacol. 2011;72:521–3.
13. Wang C, Sadhavisvam S, Krekels EH, Dahan A, Tibboel D, Danhof M, Vinks AA, Knibbe CA. Developmental changes in morphine clearance across the entire paediatric age range are best described by a bodyweight-dependent exponent model. Clin Drug Investig. 2013;33:523–34.
14. Mahmood I. Prediction of drug clearance in children: Impact of allometric exponents, body weight and age. Therap Drug Monit. 2007;29:271–8.
15. Mahmood I. Prediction of drug clearance in children from adults: a comparison of several allometric methods. Br J Clin Pharmacol. 2006;61:545–57.
16. Mahmood I, Tegenge MA. A comparative study between allometric scaling and physiologically based pharmacokinetic modeling for the prediction of drug clearance from neonates to adolescents. J Clin Pharmacol. 2019;59:189–97.
17. Mahmood I, Ahmad T, Mansoor N, Sharib SM. Prediction of clearance in neonates and infants (≤ 3 months of age) for drugs that are glucuronidated: a comparative study between allometric scaling and physiologically based pharmacokinetic modeling. J Clin Pharmacol. 2017;57:476–83.
18. Mahmood I. Prediction of drug clearance in children 3 months and younger: an allometric approach. Drug Metabol Drug Interact. 2010;25:25–34.
19. Mahmood I. Prediction of clearance, volume of distribution, and half-life of drugs in extremely low to low birth weight neonates:

an allometric approach. Eur J Drug Metab Pharmacokinet. 2017;42:601–10.

20. Mahmood I. Mechanistic versus allometric models for the prediction of drug clearance in neonates (< 3 months of age). J Clin Pharmacol. 2015;55:718–20.

21. Rowland M, Peck C, Tucker G. Physiologically-based pharmacokinetics in drug development and regulatory science. Annu Rev Pharmacol Toxicol. 2011;51:45–73.

22. Edginton AN, Theil FP, Schmitt W, Willmann S. Whole body physiologically-based pharmacokinetic models: their use in clinical drug development. Expert Opin Drug Metab Toxicol. 2008;4:1143–52.

23. Sager JE, Yu J, Ragueneau-Majlessi I, Isoherranen N. Physiologically based pharmacokinetic (PBPK) modeling and simulation approaches: a systematic review of published models, applications, and model verification. Drug Metab Dispos. 2015;43:1823–37.

24. Cao Y, Jusko WJ. Applications of minimal physiologically based pharmacokinetic models. J Pharmacokinet Pharmacodyn. 2012;39:711–23.

25. Björkman S. Reduction and lumping of physiologically based pharmacokinetic models: prediction of the disposition of fentanyl and pethidine in humans by successively simplified models. J Pharmacokinet Pharmacodyn. 2003;30:285–307.

26. van Dijkman SC, de Jager NCB, Rauwé WM, Danhof M, Della Pasqua O. Effect of age-related factors on the pharmacokinetics of lamotrigine and potential implications for maintenance dose optimization in future clinical trials. Clin Pharmacokinet. 2018;57:1039–53.

27. Cella M, Zhao W, Jacqz-Aigrain E, et al. Paediatric drug development: are population models predictive of pharmacokinetics across paediatric populations? Br J Clin Pharmacol. 2011;72:454–64.

28. Santen G, Horrigan J, Danhof M, et al. From trial and error to trial simulation. Part 2: an appraisal of current beliefs in the design and analysis of clinical trials for antidepressant drugs. Clin Pharmacol Ther. 2009;86:255–62.

29. Bonate PL, Wang T, Passier P, Bagchus W, Burt H, Lüpfert C, Abla N, Kovac J, Keiser J. Extrapolation of praziquantel pharmacokinetics to a pediatric population: a cautionary tale. J Pharmacokinet Pharmacodyn. 2018;45(5):747–62.

30. Mahmood I, Ahmad T, Mansoor N, Sharib SM. Prediction of clearance in neonates and infants (≤ 3 months of age) for drugs that are glucuronidated: a comparative study between allometric scaling and physiologically based pharmacokinetic modeling. J Clin Pharmacol. 2017;57(4):476–83.

31. Wu Q, Peters SA. A retrospective evaluation of allometry, population pharmacokinetics, and physiologically-based pharmacokinetics for pediatric dosing using clearance as a surrogate. CPT Pharmacomet Syst Pharmacol. 2019;8:220–9.

32. Box GEP. Science and statistics. J Am Stat Assoc. 1976;71:791–9.