The AAPS Journal, Vol. 16, No. 6, November 2014 (© 2014)
DOI: 10.1208/s12248-014-9667-7

Research Article

Prediction of Drug Clearance in Children: an Evaluation of the Predictive Performance of Several Models

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Received 5 June 2014; accepted 4 September 2014; published online 2 October 2014

Abstract. The objective of this study is to evaluate the predictive performance of several models to predict drug clearance in children ≤5 years of age. Six models (allometric model (data-dependent exponent), fixed exponent of 0.75 model, maturation model, body weight-dependent model, segmented allometric model, and age-dependent exponent model) were evaluated in this study. From the literature, the clearance values for six drugs from neonates to adults were obtained. External data were used to evaluate the predictive performance of these models in children ≤5 years of age. With the exception of a fixed exponent of 0.75, the mean predicted clearance in most of the age groups was within ≤50% prediction error. Individual clearance prediction was erratic by all models and cannot be used reliably to predict individual clearance. Maturation, body weight-dependent, and segmented allometric models to predict clearances of drugs in children ≤5 years of age are of limited practical value during drug development due to the lack of availability of data. Age-dependent exponent model can be used for the selection of first-in-children dose during drug development.

KEY WORDS: allometry; clearance; exponents; models.

INTRODUCTION

Children are not small adults because the differences between children of different age groups and adults are not only due to body weight or size but also due to physiological and biochemical differences resulting in different rates of drug metabolism and/or renal clearance. Therefore, dosing of drugs in children requires a thorough consideration since there are physiological differences between children and adults (1).

At least for the first decade of life, physiological changes occur rapidly but these changes are not a linear process. Many physiological factors such as tissue volumes and blood flow rates, renal and biliary excretion, as well as physico-chemical (tissue-blood partition coefficient) and biochemical (rates of drug metabolism) factors substantially influence the pharmacokinetics and pharmacodynamics of drugs. Generally, drugs are absorbed in neonates and infants much slower compared to older children and adults. Hence, the time to reach the maximum plasma concentrations is longer in the very young (2). Body weight-adjusted volumes of intra- and extracellular water are higher in neonates, infants, and children as compared to adults. Albumin and α1-acid glycoprotein concentrations are lower in neonates and infants than older children, which results in increased free fraction of drugs (3). The most important physiological difference between adults and children is in drug elimination. The metabolic pathways of drugs gradually develop with age. The enzymatic activity is less in infants and neonates compared to older children and adults (4,5). The activity of metabolic enzymes in neonates, infants, and children is about 20% to 70% of adults; as a result, most of the drugs are eliminated slowly in neonates and infants than adults (4,5). The glomerular filtration rate (GFR) in neonates is 30% to 40% of adult value (6). The GFR increases rapidly during the first 2 weeks of life because of a postnatal drop in renal vascular resistance and increase in renal blood flow. GFR then rises steadily until adult values are reached at 8 to 12 months of age (6).

Unlike first-in-adult dose where the primary concern is the safety (not necessarily efficacy), in children, both safety and efficacy are the concerns because for ethical reasons children can only be dosed when they need medicine for an underlying disease. In order to select an optimum dose in children, a pharmacokinetic (PK) study is desirable in a given age group, but there is a possibility that a PK study may be difficult to perform in children especially in preterm and term neonates as well as in infants. Therefore, under these circumstances, in order to select an optimal dose, one would like to predict the PK of a drug, especially clearance or

Electronic supplementary material The online version of this article (doi:10.1208/s12248-014-9667-7) contains supplementary material, which is available to authorized users.

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exposure (area under the curve) in children (7). However, a reasonably accurate prediction of clearance in neonates, infants, and very young children is far more difficult than the older children (7). This is mainly because in neonates and infants, the physiological events develop so rapidly that reasonably accurate prediction of pharmacokinetics of a drug in this population becomes very difficult. It should also be recognized that the etiology and course of disease may be different in children from adults. Hence, not only age but also the nature of disease can make it difficult to extrapolate PK parameters from adults to pediatric population.

Over the years, several methods have been suggested for the prediction of drug clearance in children from adult data (8–11). Alcorn and McNamara (8,9) developed a mathematical model describing the ontogeny of hepatic cytochrome P450 (CYP) enzyme-mediated clearance. The authors developed the infant scaling factor (ISF) that represents the development of a specific functional enzyme normalized to body weight relative to adult values. The ISF directly correlates adult clearance values with an infant's capacity to eliminate drugs and can be used to predict clearance in infants when adult clearance values are available. Hayton (10,11) developed a model to estimate dosing regimen in children based on the adult dosing regimen and the age and weight of the child. However, further investigation is needed to test the validity of Alcorn and McNamara as well as Hayton's models.

Allometry is widely used to predict PK parameters from animals to humans (interspecies scaling) (12,13). Allometric principles can also be applied to predict PK parameters in children, especially clearance in children from adult data. The simple allometric relationship has been shown to relate body size or weight with a parameter of interest in the field of physiology, ecology, paleontology, and pharmacokinetics (13). These relationships are related to a power function or an exponent which is diverse in nature (not fixed) (13).

The allometric equation relating body weight with a parameter of interest can be described as follows:

$$Y = aW^b \tag{1}$$

Where; Y is the parameter of interest, W is the body weight, and a and b are the coefficient and exponent of the allometric equation, respectively.

The log transformation of Eq. 1 is represented as follows:

$$\log Y = \log a + b \log W \tag{2}$$

Where $\log a$ is the y-intercept and b is the slope.

The exponents of allometry are experimentally determined from Eq. 1 or 2 (body weight against a parameter of interest). Allometric scaling based on body weight or age is simple and can be used to predict drug clearance in children by allometric extrapolation of adult clearance.

Pharmacokinetic models for modeling and simulation are widely used during drug development. These models are heavily dependent on statistics, and the predictive power of these models remains unknown because these models are rarely evaluated by external data (data which have not been used in model development). (A general practice in the evaluation of these statistically based models is bootstrapping, which may not truly reflect the accuracy of the predictive power of these models.) It is of utmost importance that the predictive power of these statistically based pharmacokinetic models be evaluated by external data. Fortunately, in recent years, some modelers with biological background have emerged, who are taking a critical look at these statistically driven models and pointing out the shortcomings and lack of predictive power of these models (14,15).

In recent years, in order to predict drug clearance in children, two models known as maturation model and body weight-dependent allometric exponent (BDE) model have been proposed. The maturation model has been applied to several drugs such as morphine (16), propofol (17), and midazolam (18). The BDE model has been applied to morphine (19), propofol (20,21), and busulfan (22).

The objective of this study is to evaluate the predictive performance of the following six models to predict drug clearance in children ≤5 years of age using external data (data not included in the model development).

1. Allometric model (data-dependent exponent)
2. Allometric model (based on a fixed exponent of 0.75)
3. Maturation model
4. Body weight-dependent allometric exponent model
5. Segmented allometric model
6. Age-dependent exponent model (ADE)

The FDA guidance on pediatrics and International Conference on Harmonization (ICH) define age groups within pediatric population as the following (23):

- Premature or preterm newborns=less than or equal to gestational age of 36 weeks
- Term newborn infants (neonates)=birth to 1 month
- Infants and toddlers=1 to 23 months
- Children=2 to 11 years
- Adolescent=12 to 16/18 years (dependent on region)

It should be noted that the abovementioned classification of age groups is arbitrary and does not necessarily coincide with the physiological changes in the pediatric population.

METHODS

From the literature, the clearance values for six drugs from neonates to adults were obtained. All six drugs were administered intravenously to the subjects. The studied drugs were alfentanil (S1–S10), amikacin (S11–S15), morphine (S16–S25), propofol (S26–S28), vancomycin (S29–S36), and oxycodone (S37–S39). These drugs were selected based on the availability of individual subjects' weight, age, and clearance data (concentration-time data of these drugs were not available to us). The chosen drugs are eliminated by extensive metabolism, exclusively by renal route or by both mechanisms (renal and hepatic). The clearance values of the studied drugs were estimated either by compartmental or non-compartmental analysis (in the original studies by the respective authors) using extensive blood sampling scheme.

Clearance data from several studies obtained from the literature across different age groups were pooled and randomly divided into two groups: data for model development and data for model evaluation. The predictive performance of the models for different age groups was evaluated by external data (data not included in the model development

but obtained from the same pooled data from which models were developed).

Drug clearance in individual subject was predicted (predictions were made from the models analyzed in this study and using external data set not included in the models) and compared with the observed clearance (CL) value in that individual. From the individual observed and predicted clearance values, the mean observed and predicted clearance values were calculated and compared. The following methods were used to develop different allometric and statistical models.

Model 1: Allometric Model (Data-Dependent Exponent)

This model was developed using the CL and body weights (BW) from neonates to adults. In this model, clearances of a drug were plotted against body weights of different age groups on a log-log scale and Eq. 3 was then used to predict drug clearance in children (≤5 years).

$$\text{CL in an individual} = a \times (\text{BW})^{b} \tag{3}$$

Where a is the coefficient and b is the exponent of the allometric equation.

Model 2: Allometric Model (Fixed Exponent 0.75)

The clearance was predicted in individual subject by using a fixed exponent of 0.75 on body weight as shown in Eq. 4. The denominator refers to a standard adult bodyweight of 70 kg

$$\text{CL in an individual} = \text{Adult CL} \times (W_C/70)^{0.75} \tag{4}$$

Where adult clearance is the mean adult clearance of a given drug obtained from the literature and W_C is the weight of a child.

Model 3: Maturation Model

Equation 3 describes a maturation model that incorporates both weight (BW) and age.

$$\text{CL} = \text{CL}_{\text{std}} \times \left(\frac{\text{BW}}{70\text{kg}}\right)^{0.75} \cdot \frac{(\text{PMA})^{\text{HillCL}}}{(\text{PMA})^{\text{HillCL}} + (\text{CL}_{\text{m at 50}})^{\text{HillCL}}} \tag{5}$$

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

Individual reported clearance values from neonates to adults were normalized to $(BW/70\ kg)^{0.75}$. The parameter estimates of the right hand side of Eq. 5 (CL_{std}, PMA_{50}, and $Hill_{CL}$) were obtained by fitting the bodyweight-normalized clearance to the maturation function. Data were analyzed by ADAPT 5 (User's Guide: Pharmacokinetic/Pharmacodynamic Systems Analysis Software. Biomedical Simulations Resource, Los Angeles, 2009) using the Bayesian maximum *a posteriori* probability (MAP) estimator. Prior distributions for the parameters were assumed to be lognormal. Graphic plots were prepared using Prism (Version 6.01, GraphPad Software Inc., Lajolla, CA).

Model 4: Body Weight-Dependent Allometric Exponent Model

The relationship between individual body weight (BW_i) and individual clearance values (CL_i) of different age groups were described by Eq. 6.

$$\text{CL}_i = \text{coefficient} \times (\text{BW}_i/70\ \text{kg})^{\text{L}\times\text{BW}_i^{(-M)}} \tag{6}$$

Where $b_{CLi} = L \times BW_i^{-M}$ defines the bodyweight-dependent exponent for clearance. The coefficient and the exponents L and M were estimated.

Individual reported clearance values from neonates to adults were analyzed by ADAPT 5 (User's Guide: Pharmacokinetic/Pharmacodynamic Systems Analysis Software. Biomedical Simulations Resource, Los Angeles, 2009) using the Bayesian maximum *a posteriori* probability (MAP) estimator. Prior distributions for the parameters were assumed to be lognormal. Graphic plots were prepared using Prism (Version 6.01, GraphPad Software Inc., Lajolla, CA).

Model 5: Segmented Model

The concept of bodyweight-dependent exponent (BDE) model can also be applied to an allometric model across several age groups with varying body weights (24). In this approach, clearance of a drug was plotted on a log-log scale against body weights for different age groups. Segmented (or piecewise) linear regression analysis was performed using the software program R (version 3.0) to obtain slopes and intercepts. The program was allowed to select the breakpoints but visual inspection was also used to ensure that the breakpoints are appropriate.

Model 6: Age-Dependent Exponent Model

In this method (25), different exponents were used for different age groups and clearance was predicted in a given age group according to Eq. 7.

$$\text{CL} = \text{Adult CL} \times (W_C/W_A)^{b} \tag{7}$$

Where "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_A is the weight of an adult standardized to 70 kg.

Exponent b in Eq. 7 is age-dependent. This method differs from method 2 (fixed exponent of 0.75) with respect to exponents. The exponents used in Eq. 7 were 1.2, 1.0, and 0.9, for ages 0–3 months, >3 months–2 years, and >2–5

years, respectively. The exponents selected in the ADE model are based from previous experience, observation, and data analysis.

STATISTICAL ANALYSIS

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

$$\%\text{error} = \frac{(\text{Predicted}-\text{observed}) \times 100}{\text{observed}} \quad (8)$$

The precision of the methods was measured by calculating the root mean square error (RMSE) according to the following equations:

$$\text{Mean Square Error (MSE)} = \frac{\sum (\text{Predicted}-\text{observed})^2}{n} \quad (9)$$

$$\text{RMSE} = (\text{MSE})0.5 \quad (10)$$

RMSE was expressed as percent of mean using Eq. 11:

$$\%\text{RMSE} = \frac{\text{RMSE} \times 100}{\text{mean observed } CL} \quad (11)$$

RESULTS

Description of the sample size and age range for model development for all six drugs is shown in Table I. In Table I, adult CL values used in models 2 and 6 are also shown. The number of subjects in the model development and in the validation model (Table II) varied and was dependent on the availability of the data. Although, the models (with the exception of models 2 and 6) were developed using data from preterm neonates to adult subjects, the models were evaluated in children from preterm neonates to 5 years old mainly because this is the age group in which prediction of clearance or a pharmacokinetic parameter is much more difficult than other age groups (older children and adolescents).

From the models, the clearances of all six drugs were predicted in an individual child, but the results are presented as mean clearance in a given age group for a given drug.

Table II. Demographics for Model Validation for the Six Drugs

Drugs	Number of subjects in validation
Morphine	*N*=82; preterm=54; 0–<1 week=14; 1 week–2 months=7; 2.5–5 years=7
Propofol	*N*=34; 1–25 days=16; 8.5–17.3 months=12; 1–2.5 years=6
Vancomycin	*N*=36; preterm=26; term=12 h–10 weeks=10
Amikacin	*N*=16; preterm=7; 4–18 months=9
Alfentanil	*N*=59; ≤3 months=15; >3 months–1 year=13; 1–5 years=31
Oxycodone	*N*=15; <1 week=7; 2.3–4.7 years=8

Individual predicted clearance values, in most of the instances, were erratic (as indicated by %RMSE) and were not in agreement with the observed clearance values. Individual prediction error of clearance ranged from 0% to more than 1000% from all methods with uncertainty in individual prediction. In this analysis, a prediction error of ≤50% (arbitrarily selected) for the mean clearance values was considered acceptable. The results of the study for the individual models are summarized below.

Model 1: Allometric Model (Data-Dependent Exponent)

The coefficients and exponents of the allometric model (model 1) are shown in Table S1. The mean predicted and observed clearance values in different age groups for the six drugs are summarized in Table III. Figure S1 represents an allometric plot of morphine (body weight *versus* clearance from preterm neonates to adults). The %CV on the coefficients and exponents of allometry ranged from 0.3% to 8% and from 3% to 11%, respectively.

A good correlation (r^2=>0.73) between body weight and clearance values was noted for all six drugs. The mean predicted clearance values were in good agreement with the observed clearance values for most drugs and age groups. Overall, the result suggests that an allometric model developed from preterm neonates to adults can predict the mean clearances of drugs in neonates and infants with a reasonable accuracy. This is not surprising since the model included the data from neonates to adults.

For six drugs, there were 16 age groups for which clearance was predicted. Out of 16 age groups, the error in the mean predicted clearance was ≤50% and ≤30% for 10 and 7 age groups, respectively (Table IV). For all six drugs,

Table I. Demographics for Model Development for the Six Drugs

Drugs	Number of subjects in the models	Adult CL*
Morphine	*N*=89; preterm=20; 0–<1 week=15; 1 week–2 months=10; 2 months–1 year=15; 2.4–10 years=10; >10–15 years=6; adults=13	1800
Propofol	*N*=52; 1–25 days=9, 3.5–11 months=10; 1–7 years=11; adolescents=8; adults=14	2000
Vancomycin	*N*=39; preterm=11; term=12 h–10 weeks=7; 1–8 years=7; adults=14	100
Amikacin	*N*=43; preterm=7; term=6; 2–17 years=20; adults=10	100
Alfentanil	*N*=48; preterm=3; 0.3–1 year=11; 1.5–14.7 years=19; adults=15	400
Oxycodone	*N*=34; <1 week=3; 1 week–2 months=6; 2–6 months=6; 6.1–9.8 years=10; adults=9	800

CL clearance
*(mL/min) were used to predict CL in children in models 2 and 6

there were 242 children and the individual prediction error >50% was observed in 39% of children.

Model 2: Allometric Model (Fixed Exponent 0.75)

Unlike the data-dependent allometric model (model 1), this method uses a fixed exponent of 0.75 for the prediction of drug clearances irrespective of the age. Individual clearance prediction from this method was highly erratic mainly in neonates and infants. The mean predicted and observed clearance values in different age groups for six drugs are summarized in Table III. The prediction error in individual neonates and infants from this method in most instances was very high ranging from >100% to >1000%.

Out of 16 age groups, the error in the mean predicted clearance was ≤50% and ≤30% for 6 and 5 age groups, respectively (Table IV) (least among all models). The individual prediction error >50% was observed in 69% (n=242) of children (highest among all models). Exponent 0.75 substantially overpredicted the clearances of all six drugs in neonates and infants. The high prediction error in neonates and infants from this method is not surprising because the method uses only adult data and a fixed exponent of 0.75, not necessarily relevant to all age groups (discussed later).

Model 3: Maturation Model

The estimated maturation model parameters (CL_{std}, PMA_{50}, and $Hill_{CL}$) for the six drugs along with parameter precision (%CV) are shown in Table S2. Percent CV was <10% for CL_{std} for all six 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 PMA_{50} was also <10% for five drugs with the exception of alfentanil (17%). The %CV for $Hill_{CL}$ showed less precision estimate for propofol (28%) and oxycodone (41%) than the remaining four drugs.

The mean predicted and observed clearance values in different age groups for the six drugs from maturation model are summarized in Table III. Figure S2 represents a maturation model plot of morphine (from preterm neonates to adults). Generally, the mean predicted clearance values were in good agreement with the observed mean clearance values. However, the individual prediction of drug clearance was erratic and the prediction error ranged from negligible to >1000%. Overall, the result suggests that a maturation model developed from neonates to adults can predict the mean clearances of drugs in neonates, infants, and children with reasonable accuracy. This is not surprising since the model included the data from neonates to adults. Out of 16 age groups, the error in the mean predicted clearance was ≤50% and ≤30% for 14 and 8 age groups, respectively (Table IV). The individual prediction error >50% was observed in 35% of children (n=242).

Model 4: Body Weight-Dependent Allometric Exponent Model

The estimated BDE model parameters (coefficients and exponents L and M) for the six drugs along with parameter precision (%CV) are shown in Table S3. The %CV was <15% for coefficients and exponent L for all six drugs, indicating a good estimate of these parameters (the predicted clearance values reconciled very well with the reported clearance values in adults with the exception of oxycodone).

Table III. Predicted and Observed Clearance (mL/min; mean±SD) of the Six Drugs in Different Age Groups by Six Models

Age group	Observed	Allometry	Exp 0.75	Maturation	BDE	Segmented	ADE*
Morphine (n=82)							
Preterm (54)*	5.5±4.1	6.9±4.9	107±32	6.3±4.1	10.1±9.3	5.0±2.4	20±10
0–<1 week (14)	41±26	20±6	180±23	23±4	35±11	14±7	46±9
1 week–2 months (7)	74±62	31±11	219±34	46±14	57±21	48±47	63±15
2–4.7 years (7)	380±110	283±62	593±60	607±64	415±72	418±70	476±57
Propofol (n=34)							
1–25 days (16)	59±43	89±29	170±46	128±56	142±67	70±40	40±15
8.5–17.3 months (12)	781±169	333±33	470±35	445±33	613±44	577±30	290±29
1–2.5 years (6)	636±119	440±92	580±90	549±86	739±89	668±72	410±111
Vancomycin (n=36)							
Preterm (26)*	1.6±1.2	1.3±0.5	5.1±1.3	1.0±0.4	1.4±0.9	0.9±0.4	0.9±0.4
12 h–10 weeks (10)	3.5±2.0	3.6±0.7	10.1±1.3	4.2±1.1	5.1±1.3	4.0±2.3	2.6±0.5
Amikacin (n=16)							
Preterm (7)*	0.45±0.21	0.79±0.30	3.76±0.92	0.64±0.34	0.66±0.46	0.49±0.29	0.54±0.2
4–18 months (9)	20±7	10±3	19±5	22±7	22±8	28±13	11±3
Alfentanil (n=59)							
<3 months (15)	19±17	27±9	45±11	15±10	25±14	22±15	13±4
>3–12 months (13)	59±27	52±14	63±12	64±20	66±23	68±20	42±11
>1–5 years (31)	131±60	112±33	109±23	131±29	148±39	123±25	94±30
Oxycodone (n=15)							
<1 week (7)	24±17	51±13	67±15	33±29	75±25	35±27	16±6
2.3–4.7 years (8)	238±76	227±31	262±33	254±32	319±20	237±30	210±31

ADE age-dependent exponent model, *BDE* body weight-dependent allometric exponent
*Age-dependent exponents in this model were 1.2, 1.0, and 0.9, for age 0–3 months, >3 months–2 years, and >2–5 years, respectively. Preterm=≤36 weeks gestational age

The %CV for exponent *M* was less precise for oxycodone (35%) than the remaining five drugs (Table S3).

The mean predicted and observed clearance values in different age groups for the six drugs from BDE are summarized in Table III. Figure S3 represents a BDE model of morphine (from preterm neonates to adults). Generally, the mean predicted clearance values were in good agreement with the observed mean clearance values. However, individual prediction of clearance was erratic and the prediction error ranged from 0 to >1000%. Overall, the BDE model predicted the mean clearances of drugs in neonates, infants, and children with a reasonable accuracy (<50% prediction error). Out of 16 age groups, the error in the mean predicted clearance was ≤50% and ≤30% for 12 and 9 age groups, respectively (Table IV). The individual prediction error >50% was observed in 39% of children (n=242).

Model 5: Segmented Allometric Model

The estimated intercepts and slopes for segmented model for the six drugs along with parameter precision (%CV) are shown in Table 4S. Morphine and vancomycin were described by three segments, whereas the remaining four drugs were describe by two segments. It should be noted that the number of segments are data-dependent and not fixed for a given drug. The %CV for the slopes of the segmented model ranged from 4% to 31%.

The mean predicted and observed clearance values in different age groups for six drugs from segmented model are summarized in Table III. Figure 4S represents a segmented model of morphine (from preterm neonates to adults). The mean predicted clearance values were in good agreement with the observed mean clearance values. This model's predictive power was slightly better for individual subjects than all other models but still quite erratic to be acceptable for individual subject's prediction of drug clearance. Out of 16 age groups, the error in the mean predicted clearance was ≤50% and ≤30% for 15 and 11 age groups, respectively (Table IV). The individual prediction error >50% was observed in 30% of children (n=242).

Model 6: Age-Dependent Exponent Model

Unlike the fixed exponent of 0.75, ADE uses different exponents for different age groups. Both in terms of mean predicted clearance and individual prediction of clearance, ADE predictive performance was far superior to the fixed exponent of 0.75. Out of 16 age groups, the error in the mean predicted clearance was ≤50% and ≤30% for 14 and 8 age groups, respectively (Table IV). The individual prediction error >50% was observed in 45% of children (n=242).

DISCUSSION

Over the years, several models have been proposed to predict drug clearances from neonates to adolescents, but these models' predictive power is rarely evaluated by external data (data not included in the model). In this study, using external data, we have evaluated the predictive performance of six models. Based on the results of this study, we noted that in many instances, one can obtain comparable mean predicted clearance (within a prediction error of 50%) values in neonates, infants, and younger children with the mean observed CL values, but the prediction error in an individual child can be substantial. The reason for this is that there is a high variability in the observed CL in children especially in children 5 years or younger. This high variability in younger children in clearance or other pharmacokinetic parameters is due to rapid physiological changes in children 5 years or younger, especially in neonates and infants. For example, propofol clearance in neonates ranged from 1 to 105 mL/min. This kind of variability will occur for almost all drugs and across all pediatric age groups which makes it difficult to predict drug clearance in an individual child.

Allometric models are generally used to predict PK parameters (clearance and volume of distribution) in pediatrics from adult data. Occasionally, by using this method, one does get reasonable prediction of the mean clearance of drugs in children ≤5 years, but most of the time, predictions of the mean clearance of drugs will be erratic with substantial error (26). On the other hand, with this approach, the mean clearance of drugs in children >5 years of age can be predicted with a reasonable accuracy (26). Mahmood (27) has proposed a method based on the adjustment of the coefficient of allometry (Boxenbaum's coefficient method) which may help in improving the predictive performance of allometry in the prediction of drug clearance in children, especially in neonates and infants from adult clearance.

In our data-dependent allometric model, we used data from neonates to adults. In this model, one assumes that a single allometric exponent describes the entire data (body weight *versus* clearance) across all age groups. This assumption, however, is incorrect.

It should be recognized that the exponents of allometry do not have any physiological or biological meaning. The exponents of allometry widely vary (exponents of allometry are data-dependent) and the range of exponents can be very wide. The exponents of allometry can be positive or negative depending on the nature of data. There is no optimum, fixed, reliable, or good exponent of allometry. Exponents <0.5 or >1.0 should not be considered either wrong or implausible. In neonates and infants, most of the time, one may observe an allometric exponent >1.0 (19–21,28).

There is no scientific basis to use any fixed exponent across all age groups. There is also no scientific basis to think that the slopes of a wide variety of data will somehow follow a same fixed number. Recent studies by dozens of investigators have shown that the concept of power law or theoretical allometry (fixed exponents of 0.25, 0.75, or 1.0) is incorrect (29–41). The theoretical allometry remains a theory as it does not reconcile with real-life observations.

As noted in this study as well as the works of several investigators (42–45), the fixed exponent of 0.75 is not suitable to predict drug clearance in children ≤5 years of age from adult data. The exponent 0.75, however, is useful for the prediction of the mean drug clearance in children >5 years of age. Two recent studies (46,47) have shown that a reasonably good prediction of the mean drug clearance from adult data can be obtained from the exponent 0.75 for children from 6 years to adolescents.

Unlike the fixed exponent 0.75 allometric model, the ADE model is based on four exponents for different age groups (as outlined in this report) and is of practical value in

Table IV. Percent Prediction Error and %RMSE in Mean Predicted Clearance by Six Models

	Allometry		Exp 0.75		Maturation		BDE		Segmented		ADE	
Drugs/age	%error	%RMSE	%error	%RMSE	%error	%RMSE	%error	%RMSE	%error	%RMSE	%error	%RMSE
Morphine												
Preterm	25	101	1845	1935	15	88	84	184	9	74	264	326
0–<1 week	51	86	339	354	44	78	15	79	66	95	12	75
1 week–2 months	58	97	196	214	38	82	23	85	35	100	15	81
2–4.7 years	26	30	56	59	60	62	9	19	15	22	25	30
Propofol												
1–25 days	51	86	188	206	117	146	141	174	19	74	32	72
8.5–17.3 months	57	61	40	45	43	48	22	29	26	33	63	66
1–2.5 years	31	34	9	17	14	20	16	22	5	15	36	40
Vancomycin												
Preterm	19	58	219	218	38	76	13	45	44	74	44	76
12 h–10 weeks	3	48	189	196	20	45	46	65	14	50	26	55
Amikacin												
Preterm	75	77	727	742	41	49	46	67	9	18	18	19
4–18 months	50	47	15	21	10	18	10	19	40	58	45	56
Alfentanil												
<3 months	42	72	137	149	21	67	32	63	16	59	32	77
>3–12 months	12	44	22	47	8	43	12	48	15	45	29	52
>1–5 years	15	50	5	46	0	46	13	50	6	46	28	55
Oxycodone												
<1 week	113	120	179	186	38	67	213	224	46	86	33	61
2.3–4.7 years	5	30	10	31	7	30	34	44	0	29	12	32

ADE age-dependent exponent model, *BDE* body weight-dependent allometric exponent, *RMSE* root mean square error

pediatric drug development and can be used to predict mean drug clearance from neonates to adolescents from adult clearance. Different exponents used in this model substantially reduced the prediction error in different age groups of children compared to a fixed exponent of 0.75 across all age groups. The exponents used in the ADE model are from previous experience and data analysis. It should be kept in mind that the exponents used in the ADE model have no physiological meaning and are arbitrary.

In this study, it was noted that the mean predicted clearance values were generally lower than the observed values by ADE model (although ≤50% prediction error in 14 out of 16 age groups was noted). The exponents 1.2 for children ≤3 months old and exponent 1.0 for children >3 months to ≤5 years old were initially suggested by Mahmood (48) based on observations, but it is practically impossible to select the best exponent for every drug and for every age group. For example, in infants ≤3 months old, the use of exponent 1.2 led to the overprediction of the mean clearance of morphine by 3.6-fold, yet the use of exponent 1.2 in infants <3 months led to a prediction error of only 32% in the mean clearance of propofol. It is suggested that a range of exponents of 1.1 to 1.2 be used for children ≤3 months old and exponents 1.0 and 0.9 be used for children from >3 months to 2 years and ≥2 to 5 years, respectively. Exponent 0.75 can be used for children >5 years of age. Overall, ADE has a practical application in pediatric drug development, but there remains uncertainty in the prediction of drug clearance in an individual child. The ADE model is fairly accurate for the mean prediction of drug clearance and simple to apply.

The practical application of allometric model lies during drug development to design pediatric clinical studies when only adult clearance values of drugs are available. Based on the current analysis and the observations of Edginton et al. (46) and Momper et al. (47) it appears that ADE is the best allometric model to predict drug clearance from adults across all pediatric age groups (preterm neonates to adolescents).

The maturation model provided a reasonably good prediction of the mean clearance of drugs in children, but like other models evaluated in this study, individual prediction was erratic and unreliable. The shortcomings of the maturation model have been discussed by Mahmood in details elsewhere (49–51).

The sigmoidal function parameter values (CL_{max}, CL_{mat50}, and $Hill_{CL}$) of a maturation model will depend and vary based on sample size, age, and weight range and are not physiologically relevant (no reconciliation with the observed values) (49–51). However, these physiologically irrelevant parameters are empirically useful for the prediction of the mean drug clearance in a given age group. In a maturation model, any real benefit of the sigmoidal part of the model will disappear after a certain age (depending on the data) and the prediction of clearance of drugs will entirely depend on body weight normalized to exponent 0.75.

A single allometric exponent cannot describe the entire data (body weight *versus* clearance or volume of distribution) across all age groups. This fact has been highlighted in four recent population PK studies (BDE models) (19–22) and by the segmented model presented in this manuscript. The studies demonstrate the importance and precision of the estimation of a mean population clearance of drugs using different exponents as a function of body weight. These models also belie the notion that age along with body weight is required to predict drug clearance in children. In fact, if one does not use the theory-based exponent (exponent 0.75) rather recognize the fact that there is no universal or fixed exponent to describe drug clearance across all age groups, then one will not need a maturation model which requires both weight and age.

The BDE models have a strong scientific basis, as in these models the exponents of allometry for drug clearance vary depending on body weight or age. In our studies, the exponents of allometry in younger children were >1 (with the exception of oxycodone) and decreased with increasing age. This observation reconciles with the observations of the BDE models (19–22) as well as Brody, Wieser, and McMohan and Bonner (28,52–54).

The BDE model for oxycodone performed poorly in children <1 week old. The predicted mean clearance was more than threefold higher than the observed mean clearance in this age group. This may be due to the lack of data for model development (Table II). The exponents of allometry ranged from 0.387 to 0.668. As seen with other drugs, an exponent >1.0 was observed in younger children, but this was not the case with oxycodone and a much lower exponent (0.668) than 1 resulted in a very high prediction of the mean oxycodone clearance in neonates (<1 week old). The range of exponents of BDE model may provide hints about the predictive performance of the BDE model.

The theme of the segmented model is the same as of the BDE model. The segmented model is a simpler version of a BDE model. The predictive performance of the segmented model was the best among all the models evaluated in this study.

Like the BDE and maturation models, segmented model can predict the mean clearance of drugs fairly well but individual clearance prediction is erratic. Overall, the practical application of the BDE, maturation models, and segmented model is limited in pediatric drug development. These models require data from a very early age (preterm or term neonates) to adults with an appropriate sample size. This kind of data will only be available after the entire drug development program including pediatric studies is over.

CONCLUSIONS

Based on the results of this study, the following conclusions can be made:

- All six models with the exception of the fixed exponent of 0.75 provided fairly good estimate (≤50% prediction error) of mean drug clearance in children ≤5 years of age. However, it is not known if the arbitrary selected prediction error in the mean CL of ≤50% should be acceptable even if these models are used as an exploratory tool in drug development.
- It should be recognized that the predictive power of the models varied from drug to drug or from one age group to the other. For example, the mean predicted clearance of morphine by maturation model was fairly accurate (prediction error=15%) in preterm neonates but the prediction error in children 2.5–

5 years was 60%. Similarly, the mean predicted clearance of morphine by ADE model was about 3.6-fold higher than the observed morphine clearance in preterm neonates, but a fairly good prediction (prediction error=8–15%) of morphine clearance was noted by the ADE model in term neonates, 1 week–2 months infants, and 2–4.7-year-old children. This kind of phenomenon was also noted with other drugs.

- The individual predicted clearance values were erratic and uncertain by all six models and are not suitable for the prediction of drug clearance in an individual child.
- Due to the requirement of extensive data (from neonates to adults), the maturation, BDE, and segmented models lack practical application during pediatric drug development since such data will not be available.
- A data-dependent allometric model does not necessarily require data from neonates to adults. An allometric model can be developed from adult data, but the predictive power of such a model in children <5 years of age remains poor. Such an allometric model, however, can be used to extrapolate drug clearance in children (≤5 years of age) from adult data using Boxenbaum's coefficient method (27).
- Age-dependent allometric model (model 6) as described in this study is useful and of practical application during pediatric drug development in order to design a first-in-children pharmacokinetic study.
- Considering the statement of the renowned statistician George E. P. Box (55) that "essentially all models are wrong but some are useful," it should be recognized that all pharmacokinetic models (allometry or statistics-based) at best are approximation of the mean PK parameters and should be used for exploratory purposes and not for confirmatory decision making because these models' predictive power remains uncertain and erratic.
- Allometric models are as good in their predictive performance of drug CL as compared to other advanced statistical models but are simpler and less time consuming.

Conflict of Interest The authors do not have any financial or conflict of interest. The views expressed in this article are those of the authors and do not reflect the official policy of the FDA or any private enterprise. No official support or endorsement by the FDA or any private enterprise is intended or should be inferred.

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