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A comparison of simple allometric and maturation models for the prediction of morphine clearance in pediatrics[1)]

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Abstract

Background: The objective of this study is to predict morphine clearance in children (preterm neonates to 10-month-old infants) by maturation models that include age and weight and to compare the predictive performance of morphine maturation models with simple allometric models.
Methods: Age, weight, and morphine clearance data were obtained from the literature. A maturation model (n=60) for morphine was developed using data from preterm and term neonates to 5-year-old children. The allometric models were developed using the same data as the maturation model. The predictive performance of the models was tested in 88 children of different age groups.
Results: The maturation and allometric models predicted morphine clearance in children with the same degree of accuracy or error. Out of 88 subjects, the prediction error of 50% or less was observed in slightly >60% of the subjects. Almost 40% of the subjects showed a prediction error >50%, 20% of which showed an error ≥100%. Although both the maturation and allometric models provided a good prediction of morphine clearance in many children, they were less accurate for many others.
Conclusions: High intersubject variability in morphine clearance probably led to less than adequate performance of the models. However, there could be many drugs for which intersubject variability in clearance might not be as high as morphine clearance and in those situations these models could perform reasonably well.

Keywords: allometry; clearance; maturation model; morphine; neonates.

Introduction

Knowledge of drug clearance is important because clearance can be used to adjust the dose in an individual irrespective of age. Numerous articles have been published outlining the developmental changes in children (1–6). These articles also emphasize that the clearance of a drug can be used for the selection of an optimal dose of a drug. The appropriate way to determine pharmacokinetic (PK) parameters in children of a given age group is to conduct a PK study in that age group, but there is a possibility that a PK study could be difficult to perform in children especially in preterm and term neonates, and infants. Under these circumstances, one would like to predict PK parameters in children of aforementioned age groups. There are several approaches that can be used to predict drug clearance in the pediatric population, such as allometric scaling, maturation models, and simulation.

Allometric models are generally used to predict PK parameters in children and in two previous studies (5, 6), Mahmood outlined several characteristics of allometric models and their application to the prediction of clearance in children of different age groups. In recent years, to predict clearance and volume of distribution of drugs in the pediatric population, a maturation model has been proposed. This model has been applied to several drugs such as morphine (7), midazolam (8), and propofol (9). However, the predictive performance of the maturation models has not been evaluated with data which were not included in building the model. Hence, the predictive performance of maturation models for clearance and volume of distribution of drugs in children of different age groups is unknown. It is also of interest and of practical value to compare a maturation model (a fixed exponent of 0.75 on body weight) with an allometric model whose exponent on body weight is data driven. Therefore, using morphine as an example, the objectives of this report are as follows:

- To develop a maturation model and an allometric model (body weight vs. clearance) for morphine clearance and compare the predictive performance of the maturation model with the allometric model.
- To develop an allometric model (body weight and gestational age vs. clearance) and compare the model with the allometric (body weight vs. clearance) and morphine maturation models.
- To predict drug clearance in children using a fixed exponent of 0.75 on body weight and adult clearance and compare the predictive performance of this model with maturation and allometric models.

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Materials and methods

Body weight, age, and clearance values for morphine were obtained from the literature (10–20). Data were randomly divided into two groups: data for model building (n=60) and data (n=88) for testing the predictive performance of the models for morphine clearance. Data for model building consisted of preterm neonates (n=23; gestation age=25–36 weeks), term neonates (n=13; gestation age=37–42 weeks), 1 week to 5-month-old infants (n=11; gestation age=39–64 weeks), and 1.9- to 5-year-old children (n=13; gestation age=139–300 weeks). The validation data consisted of preterm neonates (n=51; gestation age=25–36 weeks), term neonates (n=20; gestation age=37–42 weeks), 2-week-old to 2-month-old infants (n=8; gestation age=44–50 weeks), and >2-month-old to 10-month-old children (n=9; gestation age=50–81 weeks). The morphine observed clearance value (10–20) in an individual child was estimated either by compartmental or non-compartmental analysis. The observed morphine clearance in an individual child was compared with the predicted morphine clearance from different models in that child.

Maturation models

Model 1 Eq. [1] describes a maturation model (7) that incorporates both weight and age.

$$CL = CL_{std} \times \left(\frac{weight}{70}\right)^{0.75} \times \frac{(PMA)^{HillCL}}{(PMA)^{HillCL} + (CL_{mat50})^{HillCL}}, \quad [1]$$

where CL_{std} is the population estimate for clearance (per 70 kg body weight), *PMA* is the postmenstrual age in weeks, CL_{mat50} is the *PMA* at which clearance is 50% of the mature value, and $Hill_{CL}$ is the coefficient that describes the slope of clearance maturation.

The pediatric data (n=60) were adjusted to 70 kg body weight using the following equation:

Adjusted CL (for 70 kg body weight)=
CL in the child×(70/body weight of the child)$^{0.75}$ [2]

A sigmoidal model as shown in the right-hand side of Eq. [1] was then fitted (WinNonlin version 5.2.1; Pharsight Corporation, Mountain View, CA, USA) to the adjusted clearance for 70 kg body weight and PMA (in weeks). The CL_{std} in a 70-kg person in Eq. [1] was the maximum clearance obtained from the fit of the data. The predicted morphine clearance in an individual child, obtained from model 1 was then compared with the observed clearance value in that individual child.

Model 2 The estimated parameters for the morphine maturation model were also obtained from the study of Anand et al. (7) and were used to predict and compare morphine clearance with allometric models and model 1. The morphine maturation model of Anand et al. (7) was developed by pooling the data from two studies. One study consisted of 898 ventilated preterm neonates, of which 449 were on placebo and 449 received morphine intravenously. Data of postoperative children (0–3 years) from a previous study (7) were pooled with the preterm neonates. In the study of Anand et al., the estimated parameters for the morphine maturation model were: CL_{std}=84.2 L/h/70 kg (1404 mL/min/70 kg), CL_{mat50}=54.2 weeks, $Hill_{CL}$=3.92. The maturation model of Anand et al. was used to demonstrate the dependence of the model on sample size, age, and weight range (model 1 vs. model 2).

A scaling factor of 0.61 as proposed by Anand et al. was applied to CL_{std}, if neonates were premature (preterm). This correction factor was also applied to preterm neonates for model 1.

Model 3: Clearance vs. body weight An allometric model was developed using clearance and body weight (same data as described for maturation model; n=60) to predict clearance in children across different age groups.

CL (mL/min)=a×(body weight)^{b}, [3]

where 'a' is the coefficient and 'b' is the exponent of the allometric equation.

Model 4: Clearance vs. body weight and gestational age An allometric model was developed using clearance, age, and body weight (same data as described for maturation model; n=60) to predict clearance in children across different age groups. This analysis was done to determine if inclusion of age in an allometric model is helpful in improving the prediction of morphine clearance in children over an allometric model developed only from body weight.

CL (mL/min)=a×(body weight)^{b}×(gestational age)^{c}, [4]

where 'a' is the coefficient, 'b' and 'c' are the exponent of the allometric equation, and the gestational age is in weeks.

Model 5: Fixed exponent of 0.75 A fixed exponent allometric model was developed to predict morphine clearance in children of different age groups to demonstrate that the exponent 0.75 is not necessarily the most suitable exponent to predict drug clearance in children.

CL (L/min)=Adult CL×(weight of the subject/70)$^{0.75}$ [5]

The predicted morphine clearance in an individual child, obtained from methods 1–5, was then compared with the observed clearance value in that child.

Statistical analysis

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

$$\%error = \frac{\sum(predicted - observed) \times 100}{observed} \quad [6]$$

The bias of the methods was measured by calculating the mean prediction error (MPE) according to Eq. [7]:

$$MPE = \frac{\sum(predicted - observed)}{n}, \quad [7]$$

where '*n*' is the number of observations.

The precision of the methods was measured by calculating the mean absolute error according to Eq. [8]:

$$Mean\ absolute\ error\ (MAE) = \frac{\sum(predicted - observed)}{n} \quad [8]$$

All negative numbers obtained from Eq. [8] were converted to positive numbers.

MPE or MAE was expressed as percent of mean using Eq. [9]:

$$\%MPE\ or\ MAE = \frac{(MAE \times 100)}{mean\ observed\ CL} \quad [9]$$

Further assessment of the suitability of the methods was done by grouping the number of observations for each age group according to %error (≤30%, ≤50%, 51–99%, and ≥100%).

Results

Maturation models

The parameters of two maturation models are summarized in Table 1. The data indicate that the parameters of the maturation model could be influenced by sample size, range of body weight, and range of age. The impact was more pronounced on CL_{std} and to some extent on $Hill_{CL}$ but not on CL_{50} (weeks). Overall, the parameters of the maturation model were similar between models 1 and 2. The slight difference between these two models could be attributed to the sample size and the age range of the pediatric population.

Irrespective of the maturation models, the overall predictive power of these models in children across different age groups was almost similar (Tables 2–6). Anand et al. (7) proposed the application of a correction factor (0.61) to improve the prediction of morphine clearance in preterm neonates. This correction factor was applied to both models 1 and 2 which led to improved prediction of morphine clearance in this age group.

The mean predicted morphine clearance was comparable with the observed morphine clearance in all age groups by both models 1 and 2. However, the prediction error in morphine clearance for individual subjects might not be acceptable in practice, because the prediction error could be considered too high. Out of 88 observations (using a correction factor of 0.61 for preterm neonates), the percentage of subjects with prediction error ≤30% and ≤50% was approximately 45 and 64, respectively (Table 2). More than one-third of observations had a prediction error >50%. The MAE for both these models was >40% which could be high from a clinical perspective.

Table 1 Maturation model parameters.

Methods	Exponent	CL_{std}	CL_{mat50}, weeks	$Hill_{CL}$
Model 1	0.75	1773	57.6	4.26
95% CI	–	1492–2055	46.1–69.0	1.7–6.9
Model 2	0.75	1404	54.2	3.92
95% CI		1222–1620	50.3–60.5	3.25–4.40

CL_{std} is the population estimate for clearance (mL/min/70 kg); CL_{mat50} is the *PMA* at which clearance is 50% of the mature value, and $Hill_{CL}$ is the coefficient that describes the slope of clearance maturation. Model 1=maturation model in this study (developed from preterm neonates to children 5 years of age); model 2=the Anand et al. model (developed from preterm neonates to children 3 years of age by Anand et al.). 95% CI, 95% confidence interval.

Allometric models

The coefficients and the exponents of model 3 (clearance vs. body weight) and model 4 (clearance vs. body weight and gestational age) are presented in Table 7. The allometric models (models 3 and 4) provided similar results. Out of 88 observations, the percentage of subjects with prediction errors ≤30% and ≤50% was approximately 38 and 57, respectively (Table 2). Similar to maturation models, the MAE was >40% for models 3 and 4 (Table 2).

The worst prediction was noted for fixed exponent 0.75 (model 5). This approach substantially overpredicted morphine clearance and was highly erratic. Out of 88 observations, the prediction error was ≥100% for 84 observations (55 with >1000% prediction error).

The predictive power of the maturation (models 1 and 2) and allometric models (models 3 and 4) in terms of mean predicted clearance was comparable across all age groups (n=88, Table 2). However, a slightly better prediction of morphine clearance was noted with maturation models than the allometric models between 2-week-old and 10-month-old infants (Table 6). Overall, there is no evidence that the maturation models perform better than the allometric models or vice versa. In fact, an allometric model based on only body weight and clearance was as good as the maturation models.

Overall, the allometric and maturation models predicted morphine clearance in children of different age groups with the same degree of accuracy or error. The fixed exponent of 0.75 provided the worst result and it is evident that the sigmoidal part of the maturation model helps in improving the substantial prediction error in morphine clearance owing to the application of fixed exponent of 0.75 on body weight (Eq. [1] vs. Eq. [5]). Similarly, a data-derived (n=60) allometric exponent (1.901) provided a far superior prediction of morphine clearance in children than the fixed exponent of 0.75.

Table 2 Observed and predicted morphine clearance (mL/min) in all subjects (n=88) by different methods.

Methods	Obs CL	Pred CL	% MAE	% Bias	# Of subjects within a % error			
					≤30	≤50	51–99	≥100
Model 1	25±43	32±49	50	28	29	47	15	26
Model 1[a]	25±43	31±50	47	21	37	57	15	16
Model 2	25±43	31±42	52	25	27	38	20	30
Model 2[a]	25±43	31±50	47	23	41	54	16	18
Model 3	25±43	23±29	49	8	33	50	22	16
Model 4	25±43	22±26	51	13	32	45	26	17
Model 5	25±43	151±70	497	497	0	1	3	84[b]

Model 1=maturation model in this study; model 2=the Anand et al. model; model 3=allometric scaling (clearance vs. body weight); model 4=allometric scaling (clearance vs. body weight and gestational age); model 5=fixed exponent 0.75. [a]After using correction factor of 0.61 for preterm neonates. [b]There were 55 observations with >1000% prediction error. MAE, mean absolute error.

Table 3 Observed and predicted morphine clearance (mL/min) in preterm neonates (n=51) by different methods.

Methods	Obs CL	Pred CL	% MAE	% Bias	# Of subjects within a % error			
					≤30	≤50	51–99	≥100
Model 1	4.9±3.2	7.3±5.0	71	49	13	25	11	15
Model 1[a]	4.9±3.2	4.5±3.1	43	9	21	34	12	5
Model 2	4.9±3.2	8.6±5.5	89	75	12	17	16	18
Model 2[a]	4.9±3.2	5.2±3.3	50	7	25	32	12	7
Model 3	4.9±3.2	7.0±5.7	67	42	18	29	13	9
Model 4	4.9±3.2	7.1±5.2	67	44	17	25	16	10
Model 5	4.9±3.2	102±30	1971	1971	0	0	0	51[b]

Model 1=maturation model in this study; model 2=the Anand et al. model; model 3=allometric scaling (clearance vs. body weight); model 4=allometric scaling (clearance vs. body weight and gestational age); model 5=fixed exponent 0.75. [a]After using correction factor of 0.61 for preterm neonates. [b]A total of 46 observations with >1000% prediction error. MAE, mean absolute error.

Table 4 Observed and predicted morphine clearance (mL/min) in term neonates (n=20) by different methods.

Methods	Obs CL	Pred CL	% MAE	% Bias	# Of subjects within a % error			
					≤30	≤50	51–99	≥100
Model 1	21±14	32±8	61	54	7	10	2	8
Model 2	21±14	34±7	66	63	7	9	2	9
Model 3	21±14	29±9	47	37	10	10	4	6
Model 4	21±14	27±7	44	27	10	12	2	6
Model 5	21±14	187±23	792	792	0	0	0	20[a]

Model 1=maturation model in this study; model 2=the Anand et al. model; model 3=allometric scaling (clearance vs. body weight); model 4=allometric scaling (clearance vs. body weight and gestational age); model 5=fixed exponent 0.75. [a]A total of nine observations with >1000% prediction error. MAE, mean absolute error.

Table 5 Observed and predicted morphine clearance (mL/min) in 1-week-old to 2-month-old infants (n=8) by different methods.

Methods	Obs CL	Pred CL	% MAE	% Bias	# Of subjects within a % error			
					≤30	≤50	51–99	≥100
Model 1	48±25	60±8	44	23	3	5	1	2
Model 2	48±25	59±8	43	10	3	5	1	2
Model 3	48±25	42±13	27	12	4	6	2	0
Model 4	48±25	39±11	33	19	4	6	2	0
Model 5	48±25	218±27	351	351	0	0	0	8[a]

Model 1=maturation model in this study; model 2=the Anand et al. model; model 3=allometric scaling (clearance vs. body weight); model 4=allometric scaling (clearance vs. body weight and gestational age); model 5=fixed exponent 0.75. [a]One observation with >1000% prediction error. MAE, mean absolute error.

Table 6 Observed and predicted morphine clearance (mL/min) in >2- to 10-month-old infants (n=9) by different methods.

Methods	Obs CL	Pred CL	% MAE	% Bias	# Of subjects within a % error			
					≤30	≤50	51–99	≥100
Model 1	129±60	149±75	45	16	6	7	1	1
Model 2	129±60	130±57	35	1	5	7	1	1
Model 3	129±60	86±44	53	33	1	5	3	1
Model 4	129±60	80±39	57	38	1	2	6	1
Model 5	129±60	284±58	120	120	0	1	3	5[a]

Model 1=maturation model in this study; model 2=the Anand et al. model; model 3=allometric scaling (clearance vs. body weight); model 4=allometric scaling (clearance vs. body weight and gestational age); model 5=fixed exponent 0.75. [a] 0 Observations with >1000% prediction error. MAE, mean absolute error.

Table 7 Coefficients (mL/min) and exponents of morphine allometric scaling.

Methods	Coefficient	Exponent (on weight)	Exponent (on age)	Correlation (r^2)
Model 3	2.60	1.901	NA	0.864
Model 4	1.10	1.676	0.292	0.866

Model 3=allometric scaling (clearance vs. body weight); model 4=allometric scaling (clearance vs. body weight and gestational age). NA, not applicable.

The models were validated on 88 subjects, and out of these 88 subjects the prediction error of 50% or less was observed in slightly >60% of subjects. Almost 40% of subjects had a prediction error >50%, of which 20% of subjects had an error ≥100%. Whether or not this magnitude of error (>50% or <50%) in clearance prediction is acceptable in clinical practice is unknown.

It should be noted that at present one really does not know about the relevance of % MAE and the clinical application of the method. The %MAE, in terms of statistics, indicates the overall accuracy of the prediction. In some cases a 50% prediction error might be acceptable, whereas in other cases this might not be acceptable. All these will be based on the nature of drugs such as narrow or wide therapeutic index drugs. For example, if the prediction error in clearance is 50% then this prediction error might be acceptable for a wide therapeutic index drug for the selection of first-in-child dose. For narrow therapeutic index drugs, probably a 50% prediction error in clearance might not be acceptable, and for this class of drugs a much lower prediction error is warranted.

Discussion

Over the past few years, maturation models have been developed for several drugs to predict drug clearance in pediatrics. Although the predictive performance of these models has not been tested using external data (data not included in the development of the model), the model is being advocated as a tool for the prediction of clearance and volume of distribution in pediatrics (7–9). Therefore, it is important and of practical value that these models be validated with external data.

Although, in this study, the maturation and allometric models provided the same magnitude of prediction error (in terms of mean) for morphine clearance across different age groups, it is important to recognize that the models predicted morphine clearance in a given individual with different degrees of accuracy or error. For example, in a subject the prediction error in morphine clearance was 49%, 76%, and 17%, by model 1, model 2, and model 3 (allometry), respectively. Similarly, in another subject, the prediction error in morphine clearance was 14%, 36%, and 35%, by model 1, model 2, and model 3 (allometry), respectively. This type of observation was noted across the entire age range. Therefore, even though the overall predictive performance of the models was similar, it is difficult to assess a priori which model will provide a fairly reasonable prediction in a given subject.

Although the morphine allometric and maturation models provided reasonably good predictions of morphine clearance in some children; however, owing to high variability observed in morphine clearance, the predicted clearance can be highly erratic in most of the children owing to high variability in the observed clearance. Two children can be approximately of the same age and body weight, yet their clearances can be substantially different. For example, two preterm neonates of 29 weeks gestational age had body weights of 1.36 and 1.0 kg and the observed morphine clearance in these two neonates was 7.5 and 2.2 mL/min, respectively. The prediction error by model 1 was 37% and 72%, by model 2 was 22% and 112%, and by allometry (model 3) was 37% and 20%, respectively. This type of observation will be associated with every drug and in every age group and this variability will be much higher in neonates and infants than younger or older children. This makes it almost impossible to predict clearance of a drug with reasonable accuracy by using any type of model.

The major flaw of the maturation model is the use of a fixed exponent of 0.75 on body weight. There is no logic to use any fixed exponent on any physiological or PK parameter, because the exponents of allometry are neither physiological nor universal (21–29). Furthermore, because age and weight are well correlated parameters, the inclusion of both weight and age in a model will not necessarily improve the prediction of a parameter if only weight or age is used (6). This is evident in this study as the allometric model based on only weight, allometric model based on weight and age, and the maturation model based on weight and age provided similar results. The predictive power of the maturation model could be improved by allowing the model to freely iterate the exponent instead of a fixed exponent.

It should be recognized that there are substantial physiological differences among children of different ages and adults. Therefore, in the development of any model these changes must be considered. Incorporation of both weight and age in a model might not account for real physiological age differences, because both of these parameters are physical and are well correlated. In other words, the models must be developed separately for different age groups.

Conclusions

Overall, this study indicates that the morphine maturation model does not provide any practical advantage in the prediction of morphine clearance over the simple allometric model (clearance vs. body weight). Furthermore, there are several caveats with the maturation model:

- The sigmoidal part of the morphine maturation model is of little value after the first year of life because the model becomes dependent on body weight, normalized clearance to a 70-kg subject, and exponent of 0.75. In reality, the process of morphine maturation clearance does not stop at age one (30). Thus, the model does not represent any mechanistic or physiological process.

- The major flaw of the morphine maturation model is the use of the fixed exponent of 0.75 on body weight, because there is no justification to fix the exponent of body weight. As observed in this study and several other studies (5, 6, 27–29), the use of the fixed exponent of 0.75 produces substantial prediction error in drug clearance (especially in neonates and younger children), and the role of the sigmoidal part of the maturation model appears to correct this substantial error. Therefore, there is no need of a maturation model if the exponent on body weight is not fixed (e.g., 0.75).
- Generally, weight and age are well correlated and a model which incorporates both body weight and age will not necessarily improve the prediction of a PK parameter in children as compared to the prediction obtained based on body weight or age alone (as also observed in this study, model 4).
- Out of 88 subjects, the prediction error of 50% or less was observed in slightly >60% of subjects. Almost 40% of the subjects showed a prediction error >50%, 20% of which showed an error ≥100%. Clinical significance of prediction error of >50% or >100% in clearance of a given drug in the pediatric population to adjust the dose is unknown.
- The predictive performances of the maturation and allometric models for other drugs should be extensively evaluated. If the performances of both these models are found to be similar then the allometric model is the model of choice owing to the ease of model building and simplicity. The predictive performance of allometric models can be substantially improved by developing different models for different age groups. At present, this is not known about the maturation model.
- Although the predictive performances of the maturation and allometric models for the prediction of morphine clearance in an individual subject are moderate, this should not lead to the abandoning of these models. In the case of morphine clearance, intersubject variability is very high (coefficient of variation=172%; n=88) which probably has led to less than adequate performance of the models. There are many drugs for which intersubject variability might not be as high as morphine and in those situations these models might perform reasonably well. This view, however, must be thoroughly tested.

Conflict of interest statement

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