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Prediction of absolute bioavailability of medicines in children: based on predicted pediatric clearance from adults

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Abstract

Aim: The objective of this study was to evaluate the predictive performance of a proposed method to predict absolute bioavailability of medicines in children (infants to adolescents).

Methods: From the literature, systemic and oral clearances as well as absolute bioavailability values for 15 medicines (28 observations across different age groups) from infants to adults were obtained. Systemic and oral clearances of these medicines in children were predicted using age-dependent exponent (ADE) allometric model using observed adult clearance values. Then using the predicted clearance values, absolute bioavailability was predicted in children. The predictive performance of the proposed method was evaluated by comparing the predicted absolute bioavailability of the studied medicines with the observed absolute bioavailability in children.

Results: The results of the study indicated that the ADE model provided a good prediction of systemic and oral clearances in children from adult clearance values [89% and 82% observations within 0.5–1.5-fold prediction error following intravenous (IV) and oral administration, respectively]. The predicted absolute bioavailability by the proposed method was within 0.5–1.5-fold prediction error for 93% observations.

Conclusions: This study indicated that it was possible to estimate absolute bioavailability of medicines in children with acceptable accuracy (within 0.5–1.5-fold prediction error) by the proposed method. The estimated absolute bioavailability in children could be useful in designing a first-in-children dose during pediatric drug development.

Keywords

Pediatrics, absolute bioavailability, allometry, clearance, age-dependent allometric model

Introduction

Absolute bioavailability refers to the fraction of a dose that reaches the systemic circulation following extravascular (oral, intramuscular, or subcutaneous) administration of a medicine as compared to an

intravenous (IV) dose. After IV administration of a dose, absolute bioavailability is equal to 1.0 because the total amount of medicine is available in the systemic circulation [1].

Absolute bioavailability is the ratio after extravascular and IV administration, adjusted for differences in the dose. For example, following an IV and oral administration of a drug, absolute bioavailability can be calculated as follows [1]:

$$Absolute\ bioavailability = \frac{AUC\ (oral)/dose}{AUC\ (IV)/dose} \quad (1)$$

Where AUC is the area under the curve following IV and oral administration.

In order to select a reasonably accurate dose for first-in-children clinical trials one would like to predict pharmacokinetic (PK) parameters in children from adult data. Then these predicted PK parameters can be used to design a first-in-children dose in clinical trials. The important PK parameters are clearance, volume of distribution, and half-life [1, 2]. Among all of these three PK parameters, clearance is the most important PK parameter as it represents the exposure of a medicine (clearance = dose/AUC). Therefore, the knowledge of clearance of medicine in designing a first-in-children dose during pediatric drug development is of practical value [2, 3].

Allometric scaling based on body weight or age is simple and can be used to predict PK parameters in children by allometric extrapolation of adult PK parameters [4–6]. Allometric methods have been applied to predict the clearances of medicines following IV and oral administration and the predictive performance of these allometric models were within acceptable prediction error (0.5–1.5-fold) [4–6].

The oral absorption of medicines varies across age due to differences in the anatomical and physiological characteristics of the gastrointestinal tract, dietary habits, blood flow through the gut and the liver, and the enzymatic activities of metabolizing enzymes in the liver and gut [7]. All these physiological processes along with the physicochemical properties (formulation) of medicines become even more complicated in the pediatric population especially, in younger children generally less than 5 years of age [7]. Therefore, the rate and the extent of the absorption of a medicine may vary from one age group to the other.

Dedicated PK studies following oral and IV administration allow the accurate estimation of absolute bioavailability in children across different age groups. The dedicated PK studies are generally based on several blood samples (5–8 blood samples) depending on the half-lives of medicines. For short half-life (3–4 hours) medicines, one does not need to take many blood samples. However, in neonates, infants, and toddlers it is difficult to take more than 2 or 3 blood samples. Therefore, few blood samples (generally 1 to 2) are taken from these age groups and then such a sparse blood sampling scheme can be used by pooling concentration-time data from neonates to adults and applying a population PK approach to predict PK parameters such as clearance and volume of distribution. If oral and IV data are available then absolute bioavailability can be reliably (since population PK approach is data-dependent) determined from such a sparse sampling scheme in adults and children.

It is not ethical to administer medicines by both IV and oral routes to children just for the sake of determination of absolute bioavailability in children. Therefore, one approach may be the prediction of absolute bioavailability in children. Due to the aforementioned complexities [7], prediction of absolute bioavailability in children from adults may not be straightforward but using some appropriate method(s) it is possible to predict absolute bioavailability with reasonable accuracy in children from adults.

The objective of this study was to evaluate the predictive performance of a proposed method for the prediction of absolute bioavailability in children (infants to adolescents). The method is based on the predicted clearance of medicines in children from adults using allometric scaling.

Materials and methods

From the literature, systemic and oral clearance and absolute bioavailability values for 15 medicines from infants to adults were obtained [8–48]. The following method was used for the prediction of absolute bioavailability from infants to adolescents.

Prediction of clearance: age-dependent exponent (ADE) allometric model

In the first step of the analysis, both the systemic and oral clearances of medicines in children were predicted allometrically from adult clearance and the predicted clearance values were compared with the observed clearances of medicines. The clearance values in adults and children (based on extensive sampling) of the studied medicines across the age groups were estimated either by compartmental or non-compartmental analysis (in the original studies by the respective authors) and were used as the observed clearance values.

In order to predict the clearance of the studied medicines, different allometric exponents were used for different age groups and clearance was predicted in a given age group according to equation 2.

$$Clearance\ in\ a\ child = a \times (weight\ of\ the\ child/70)^{b} \quad (2)$$

Where 'a' is the coefficient (adult clearance), 'b' is the exponent of the allometric equation, and 70 is the standard body weight of an adult. Exponent 'b' in equation 2 is age-dependent. The exponents used in equation 2 were 1.2 for preterm neonates (≤ 3 months of age), 1.1 for term neonates (≤ 3 months of age), exponent of 1.0 for children > 3 months to 2 years, 0.9 for >2–5 years old children, and exponent 0.75 for children > 5 years of age. The application and concept of ADE have been previously described in several manuscripts [4–6].

Prediction of absolute bioavailability in children

The absolute bioavailability of a medicine in a specific age group was predicted as follows:

$$Absolute\ bioavailability = clearance_{(IV)}/clearance_{(oral)} \quad (3)$$

The IV and oral clearance values in equation 3 are the predicted clearance values in children. In equation 1, it was mentioned that AUC is generally used for the estimation of absolute bioavailability. However, clearance is another parameter that can also be used to predict absolute bioavailability as shown in equation 3.

Statistical analysis

Percent error between the observed and predicted clearance and absolute bioavailability values were calculated according to the following equation:

$$Error\ (\%) = \frac{(predicted - observed) \times 100}{observed} \quad (4)$$

Generally, in the literature, a 2-fold prediction error is considered an acceptable prediction error for PK parameters. However, this author considers a 2-fold prediction error too high and in many instances of little practical value. Therefore, in this study, a ≤ 50% prediction error (0.5–1.5-fold) for clearance and absolute bioavailability was considered a reasonably good prediction. This acceptance criteria are also based on the wide variability in the observed absolute bioavailability in children and adults.

Results

Tables 1 and 2 are the summary of the results in terms of number and percent observations and prediction with fold errors for clearance and absolute bioavailability, respectively. In Tables 3 and 4, the predicted and observed absolute bioavailability and clearance values are shown, respectively. The clearance and absolute bioavailability of all 15 drugs (28 observations across different age groups) were predicted and compared with the observed values.

Following IV administration (n = 28), 89% clearance values were within 2-fold and 0.5–1.5-fold prediction error (Table 1). Following oral administration (n = 28), 86% and 82% clearance values were within 2-fold and 0.5–1.5-fold prediction errors, respectively (Table 1).

Table 1. Number of observations within fold errors (predicted clearance following IV and oral administration)

Fold error	IV (n = 28)	Oral (n = 28)	IV (%)	Oral (%)
0.5–2	25	24	89	86
0.5–1.5	25	23	89	82
0.7–1.3	21	16	75	57
> 2	0	0	0	0
< 0.5	2	4	7	14

IV: intravenous

The predicted absolute bioavailability (n = 28) in children was 100% and 93% within 0.5–2 and 0.5–1.5 prediction error, respectively. The absolute bioavailability was predicted fairly accurately in children based on predicted IV and oral clearance (Table 2).

Table 2. Number of observations within fold errors (predicted absolute bioavailability)

Fold error	Absolute bioavailability (n = 28)	Absolute bioavailability (%)
0.5–2	28	100
0.5–1.5	26	93
0.7–1.3	21	75
> 2	0	0
< 0.5	0	0

Absolute bioavailability of ketoprofen in children was calculated as follows: the IV clearance values of ketoprofen in children (7–93 months) were available (0.07 L/hr/kg, [42]). In children, 0.5–2 years and >2–7 years the IV clearance was projected to be 12 mL/min and 22 mL/min, respectively, from children 7–93 months. In children 7–93 months the IV clearance was 23 mL/min (PK based value) (Table 4). The clearance following oral administration in children (6–69 months) was available (0.09 L/hr/kg, [43]). The oral clearance was projected in children 7–93 months as 30 mL/min. Using these clearance values and equation 3, absolute bioavailability was predicted in children of different age groups.

Discussion

Clearance of a medicine is a function of maturation of organs, as age increases the clearance of the medicine increases [2, 49]. The physiological parameters, such as organ weights, blood flow, enzymatic activities, etc., can be allometrically related to body weight or age (since age is well correlated to body weight) with variable exponents [2, 4–6]. The allometric exponents of PK parameters widely vary with age or weight. The so-called theoretical exponent 0.75 does not represent the true exponents of maturational changes and substantial errors in the prediction of drug clearance, especially in younger children occur [4–6] when exponent 0.75 is used.

The ADE model as described here was proposed by Mahmood to predict pediatric clearances of medicines following IV and oral administration from pre-term neonates to adolescents [4–6]. In neonates, infants, and toddlers, physiological changes develop very rapidly but these changes are not linear. Therefore, considering these rapid physiological changes, a single allometric exponent does not describe the clearance versus body weight or age across all age/weight groups. Therefore, a multi-exponent model in terms of ADE was developed [4–6].

In this study, the clearances of 2 and 4 medicines were under-predicted (predicted/observed ratio < 0.5) following IV or oral administration, respectively. Especially, the ratio of predicted clearance of digoxin was only 0.2 (the lowest ratio among all medicines). This can be explained as follows.

Table 3. Predicted and observed absolute bioavailability in children

Medicines	Age	Observed F mean (%)	Observed range (%)	Predicted F (%)	Ratio of predicted/observed	References
Midazolam	Adult	48	32–64	NA	NA	[8]
	Preterm	49	12–100	38	0.77	[9, 10]
	0.5–2 years	37	±21	42	1.14	[11]
	5.5–6 years	27	NA	42	1.57	[12]
Famotidine	Adult	45	38–51	NA	NA	[13]
	11–15 years	51	NA	45	0.88	[14]
	0–1 year	42	NA	45	1.07	[15]
Voriconazole	Adult	83	75–94	NA	NA	[16]
	2–<6 years	44	NA	79	1.79	[17]
	6–<12 years	91	NA	79	0.86	[17]
Diclofenac	Adult	54	NA	NA	NA	[18]
	1–12 years	70	NA	60	0.85	[19, 20]
Cyclosporine	Adult	22	±7.4	NA	NA	[21]
	1.1–2.5 years	22	11–35	19	0.86	[22]
Cefetamet	Adult	41	24–64	NA	NA	[23]
	3–7 years	49	29–70	39	0.79	[24]
	>7–12 years	38	36–47	39	1.02	[24]
	3.5–17.3 months	38	±19	39	1.02	[25]
Zidovudine	Adult	75	60–95	NA	NA	[26]
	Term < 14 days	89	±19	75	0.84	[27]
	Term > 14 days	61	±19	75	1.23	[27]
Azithromycin	Adult	43	±13	NA	NA	[28]
	0.5–2 years	27	NA	39	1.43	[29, 30]
	>2–5 years	37	NA	45	1.20	[29, 30]
	7–12 years	52	NA	45	0.86	[29–31]
Busulfan	Adult	80	47–103	NA	NA	[32]
	1.4–6 years	68	22–120	73	1.07	[32]
Cimetidine	Adult	60	30–100	NA	NA	[33]
	4–13 years	54	51–57	59	1.09	[34]
Digoxin	Adult	74	63–84	NA	NA	[35]
	Newborn infants	72	52–79	73	1.02	[36]
Clonidine	Adult	88	±9	NA	NA	[37]
	3–10 years	55	NA	88	1.62	[38]
Ranitidine	Adult	51	35–65	NA	NA	[39]
	3.5–16 years	48	22–96	46	0.95	[40]
Ketoprofen	Adult	≥92	NA	NA	NA	[41]
	7–93 months	77	NA	92	1.20	[42, 43]
	0.5–2 years	80	NA	92	1.15	[42–44]
	>2–7 years	69	NA	92	1.34	[42–44]
Itraconazole	Adult	19	NA	NA	NA	[45, 46]
	0.5–2 years	32	NA	20	0.63	[47, 48]
	>2–5 years	35	NA	22	0.62	[47, 48]
	>5–12 years	30	NA	22	0.73	[47, 48]

F: absolute bioavailability; NA: not available

Digoxin PK was conducted in newborn infants with heart failure whereas; the PK study in adults was conducted in subjects without cardiac disease. Blood samples in the infants were collected till 8 hours and in adults till 96 hours. Thus, the sampling scheme had impact on the clearance of digoxin in neonates compared with adults. A shorter sampling scheme in children indicated a higher clearance which may not be true clearance had the samples were taken a little bit longer. Therefore, the predicted clearance of

Table 4. Predicted and observed clearance values in children

Medicines	Age	Observed clearance (mL/min)		Predicted clearance (mL/min)		Ratio = predicted/observed	
		IV	Oral	IV	Oral	IV	Oral
Midazolam	Adult	323	763	NA	NA	NA	NA
	Preterm	1.8	2.9	2.0	5.2	1.10	1.80
	0.5–2 years	52	286	36	85	0.69	0.30
	5.5–6 years	159	585	114	270	0.72	0.46
Famotidine	Adult	463	1,030	NA	NA	NA	NA
	11–15 years	400	718	360	800	0.90	1.11
	0–1 year	55	131	66	147	1.20	1.12
Voriconazole	Adult	254	323	NA	NA	NA	NA
	2–<6 years	102	232	92	117	0.90	0.50
	6–<12 years	171	279	137	174	0.80	0.62
Diclofenac	Adult	263	499	NA	NA	NA	NA
	1–12 years	153	218	103	173	0.67	0.79
Cyclosporine	Adult	317	1,683	NA	NA	NA	NA
	1.1–2.5 years	113	518	57	305	0.51	0.59
Cefetamet	Adult	155	399	NA	NA	NA	NA
	3–7 years	50	230	54	138	1.07	0.60
	>7–12 years	79	393	94	242	1.19	0.62
	3.5–17 months	18	48	21	54	1.16	1.12
Zidovudine	Adult	1,377	1,832	NA	NA	NA	NA
	Term < 14 days	22	32	28	37	1.25	1.15
	Term > 14 days	76	85	76	101	0.99	1.18
Azithromycin	Adult	817	1,910	NA	NA	NA	NA
	0.5–2 years	166	606	118	306	0.71	0.50
	>2–5 years	280	749	214	480	0.76	0.64
	7–12 years	624	1,191	527	1,172	0.84	0.98
Busulfan	Adult	175	240	NA	NA	NA	NA
	1.4–6 years	57	99	58	79	1.01	0.80
Cimetidine	Adult	495	840	NA	NA	NA	NA
	4–13 years	302	559	236	400	0.78	0.71
Digoxin	Adult	192	262	NA	NA	NA	NA
	Infants	39	55	8	11	0.21	0.20
Clonidine	Adult	260	292	NA	NA	NA	NA
	3–10 years	85	155	102	114	1.20	0.74
Ranitidine	Adult	677	1,485	NA	NA	NA	NA
	3.5–16 years	568	1,183	526	1,154	0.93	0.98
Ketoprofen	Adult	83	90	NA	NA	NA	NA
	7–93 months	23	30	32	35	1.41	1.17
	0.5–2 years	12	15	12	13	0.99	0.86
	>2–7 years	22	32	31	34	1.42	1.06
Itraconazole	Adult	337	1,762	NA	NA	NA	NA
	0.5–2 years	173	541	44	219	0.25	0.40
	>2–5 years	160	465	123	563	0.76	1.21
	>5–12 years	298	991	173	787	0.58	0.79

For clearances same references as of absolute bioavailability. IV: intravenous; NA: not available

digoxin in children in neonates and infants was substantially lower. Furthermore, the disease state would have also impacted the clearance of digoxin in the neonates. This example demonstrates that sampling time points and disease state(s) between adults and children (especially, neonates and infants) may have substantial impact on the PK of a medicine which a model may not pick. These factors may also over-estimate the predicted PK parameters of a medicine in children.

The impact of gut microbiota and gut flora ontogeny on drug metabolism requires consideration since these can influence the absorption of medicines [50–52]. After oral dosing to adults, digoxin is partially eliminated as reduced metabolites containing a saturated lactone ring (e.g., dihydrodigoxin). This reaction is due to the anaerobic bacteria of the gut flora. Linday et al. [53] evaluated the PK of digoxin in more than 200 subjects, age ranging from 3.5 weeks to adults. The authors measured excretion of digoxin reduced metabolites at different ages in urine. Subjects were classified as excretors when digoxin reduced metabolites accounted for at least 5% of the total drug-related material. Reduced metabolites were not detected below 8 months of age and in adults, these metabolites were observed after 16 months.

It should be recognized that absolute bioavailability is not age-dependent and many factors including age-dependent metabolism can impact absolute bioavailability. For example, midazolam is extensively metabolized by CYP3A4, and absolute bioavailability of midazolam in adult healthy subjects is 50% [8]. Another study indicates a midazolam absolute bioavailability in adults from 24% to 38% [54]. de Wildt et al. [9] noted that absolute bioavailability of midazolam in preterm infants was 49%. The authors attributed this to a 10-fold lower oral clearance of midazolam in infants than older children and adults. In Table 1, the absolute bioavailability of midazolam in preterm neonates, children 0.5–2 years, 5.5–6 years, and adults are shown. The higher absolute bioavailability of midazolam in preterm neonates than adults is attributed to the substantial lower oral clearance of midazolam in the neonates [7, 9].

In an allometric model, a parameter of interest is related to body weight but it is difficult to justify that an allometric relationship may exist between body weight and absolute bioavailability. In a study, it was shown that interspecies scaling of absolute bioavailability versus body weight provided erratic and inconsistent prediction of absolute bioavailability from animals to humans [55]. As mentioned earlier, absolute bioavailability is not age-dependent hence, absolute bioavailability can be similar, higher, or lower in children across age groups compared with adults (Table 3).

The proposed method in this study requires adult systemic and oral clearance data which are generally available. Using the adult IV and oral clearance values, the clearances of medicines were predicted in children using ADE model. In this study, 89% predicted clearance values of medicines in children following IV administration were within 0.5–2-fold and 0.5–1.5-fold prediction error. Following oral administration, 86% and 82% predicted clearance values were within 0.5–2-fold and 0.5–1.5-fold prediction error, respectively. Overall, the clearances of medicines were predicted fairly accurately for both routes of administration using ADE model. Such good prediction of clearance is important because these clearance values are then used for the prediction of absolute bioavailability in children.

The predicted absolute bioavailability was within 0.5–2-fold, 0.5–1.5-fold, and 0.7–1.3-fold prediction error for 100%, 93%, and 75% observations, respectively. The fact that 75% observations were within 30% prediction error indicates the robustness of the method for the prediction of absolute bioavailability of medicines in children. It should be recognized that all models carry errors in their predictive performance and the proposed model is not error free. There will be many instances where prediction of absolute bioavailability in children may not reconcile well with the observed absolute bioavailability. Overall, the magnitude of prediction error in this study is acceptable because there is a high variability in absolute bioavailability of medicines as noted in this study (adults as well as children) and the observed range of absolute bioavailability is too wide (Table 3). Considering the high variability in absolute bioavailability across individual subjects, a 50% prediction error should be considered acceptable. This study also emphasizes that absolute bioavailability can be reasonably estimated in children by extrapolating clearance values from adults.

Absolute bioavailability is generally not determined in children especially, in neonates, infants, and younger children (< 5 years of age) hence, data are scarce in these age groups. Although this study is based on a small data set (n = 28 observations), the proposed method provides a reasonably accurate prediction of absolute bioavailability of medicines in children which may be helpful in designing a pediatric oral dose in early drug development. Considering high variability in the observed absolute bioavailability of medicines, the proposed method is quite robust. In conclusion, it is possible to predict absolute

bioavailability of medicines in children by using predicted pediatric clearances from adult IV and oral clearances according to equation 3.

Abbreviations

ADE: age-dependent exponent

IV: intravenous

PK: pharmacokinetic

Declarations

Author contributions

IM: Conceptualization, Data curation, Writing—original draft.

Conflicts of interest

The author has no conflicts of interest.

Ethical approval

Since this study analyzed secondary data, ethical approval is not required.

Consent to participate

Not applicable.

Consent to publication

Not applicable.

Availability of data and materials

Requests for accessing the datasets should be directed to Iftekhar Mahmood (Iftekharmahmood@aol.com).

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