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# Prediction of drug clearance in children 3 months and younger: an allometric approach

**Iftekhar Mahmood***

Division of Hematology, Office of Blood Review and Research (OBRR), Center for Biologic Evaluation and Research, Food and Drug Administration, Rockville, MD, USA

## Abstract

**Background:** Sometimes it might not be possible to conduct a pharmacokinetic (PK) study in neonates and infants. Under these circumstances, one would like to predict PK parameters in this age group. Because drug clearance is the most important PK parameter, the objective of this study was to describe an allometric method to predict drug clearance in children ≤3 months.

**Methods:** In total, 43 drugs (107 observations) were randomly selected for this study. The age of the children ranged from 0 to 1 year. Children were divided into two groups: ≤3 months and ≥3 months to 1 year. Drug clearance (CL) in children was predicted using the following equation: CL in the child=adult CL×(weight of the child/70)$^{0.75 \text{ or } 1.0 \text{ or } 1.2}$.

**Results:** The results of the study indicated that the exponent 1.2 performs better in the prediction of drug clearance than exponent 1.0 or 0.75 for children ≤3 months. By contrast, exponent 1.0 provided better prediction for children ≥3 months to 1 year than exponent 1.2. Exponent 0.75 provided the worst results leading to substantial prediction error in children 0–1 year (in many instances more than 1000% prediction error).

**Conclusions:** Overall, it appears that exponent 1.2 is the best method out of three methods for reasonably accurate prediction of drug clearance in children ≤3 months old. However, exponent 1.2 will underpredict drug clearance in children older than 3 months. The suggested approach could be used to support the choice of the initial dose in clinical trials for children ≤3 months old.

**Keywords:** allometric scaling; clearance; exponents; neonates and infants; pharmacokinetics.

*Corresponding author: Iftekhar Mahmood, Division of Hematology, Office of Blood Review and Research (OBRR), Center for Biologic Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852, USA
Phone: +1-301-827-6153, E-mail: iftekhar.mahmood@fda.hhs.gov
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## Introduction

Dosing of drugs in children requires thorough consideration of the physiological differences between children and adults. Owing to the advent of pediatric exclusivity and requirements for conducting clinical studies in children, the current emphasis is on finding safe and efficacious doses of drugs for children on the basis of pharmacokinetic knowledge of drugs in adults. There can be two scenarios for the selection of dose in the pediatric population (1):

- When no dosing or pharmacokinetic information are available in the children population but this information is available in the adult population. In this case, one asks how to select a safe and efficacious first-in-children dose? This question is generally raised before initiating first-in-children clinical trial.
- When both dosing and pharmacokinetic information are available in children. In this case, one asks how to select a first-in-child dose (individual drug therapy)? This question is mainly raised in clinical settings where an individual child needs treatment.

In both the aforementioned situations, one can predict pharmacokinetic parameters using a suitable allometric approach. Clearance of a drug is the most important pharmacokinetic parameter and over the years, several methods have been suggested for the prediction of drug clearance in children from adult data. Alcorn and McNamara (2, 3) developed a mathematical model describing the ontogeny of hepatic cytochrome P450 enzyme-mediated clearance. The authors developed the Infant Scaling Factor, which is a specific functional enzyme normalized to body weight relative to adult values. Hayton and colleagues (4, 5) developed a maturation model to estimate dosing regimen in children based on the adult dosing regimen and the age and weight of the child. Further investigation, however, is needed to test the validity of the Alcorn and Hayton models.

Allometric scaling is extensively used for the prediction of pharmacokinetic parameters from animals to humans and can be used for the selection of first-in-human dose (6–10). Allometric scaling can also be used to predict a pharmacokinetic parameter in children from adult data or once pharmacokinetic information of a drug is available in children then an allometric model can be developed to predict a pharmacokinetic parameter in children within the age group from which the model has been developed (11, 12). Allometric scaling is simple and can be easily done once information on the pharmacokinetics of a drug in adult or/and children is available.

The simple allometric relationship has been shown to relate body size with a parameter of interest in the field of physiology, ecology, paleontology, and pharmacokinetics (13). These relationships are described by a power function as shown in Eq. [1].

$$Y = aW^b \quad [1]$$

where 'Y' is the parameter of interest, 'a' is the coefficient, 'W' is the body weight, and 'b' is the exponent of the allometry.

Eq. [1] has been extensively used to predict pharmacokinetic parameters such as clearance, volume of distribution, and half-life from laboratory animals to humans (14). The allometric principles, however, can also be applied to predict drug clearance in children. It has been suggested (15) that the clearance of a drug in children can be predicted according to the following equation:

$$\text{CL in the child (mL/min)} = \text{Adult CL} \times (\text{weight of the child}/70)^{0.75} \quad [2]$$

where, 70 (in kg) is the standard weight of an adult and adult clearance (CL) can be normalized based on 70 kg adult body weight.

However, exponent 0.75 (as shown in Eq. [2]) is not the most optimum exponent for the prediction of drug clearance in children. A systematic evaluation of the exponent 0.75 by Mahmood (16) indicated that the exponent 0.75 is not suitable for the prediction of drug clearance across all age groups (especially in neonates and infants). In his study, Mahmood (16) evaluated the predictive performance of not only a fixed exponent of 0.75 but also other exponents such as 0.85 and 0.80 on the body weight. All three exponents (0.75, 0.80, and 0.85) produced the same degree of accuracy or uncertainty in the prediction of clearance in children, suggesting that the notion that 0.75 is the most suitable allometric exponent for the prediction of drug clearance in children is inaccurate. The prediction of drug clearance in neonates, infants, and very young children was highly erratic when exponent 0.75 was used and the prediction error in some cases reached to thousands of percent. In his study, Mahmood also noted that the exponent 0.75 predicted drug clearance with a reasonable degree of accuracy when the children were older than 5 years. On the basis of his analysis, Mahmood (16) suggested that for children ≤1 year old, no exponent should be used on the ratio of children and adult body weight (Eq. [2]). Basically, this approach suggests that the prediction of drug clearance in children ≤1 year old can be obtained far more accurately by using body weight normalized clearance than using a fixed exponent of 0.75 on body weight. For example, if the clearance of a drug is 10 mL/min/kg in a 70-kg adult, then the projected clearance in a 3-kg child (1 year or younger) should be predicted as 30 mL/min rather than 66 mL/min (obtained from Eq. [2]). The accuracy of body weight normalized predicted clearance of drugs in children 1 year or younger has been demonstrated by Mahmood (16).

Although Mahmood's approach for the prediction of drug clearance in children ≤1 year old provided substantially better prediction than the fixed exponent of 0.75, the prediction error in some children remained high. A thorough review of the data indicated that in children ≤3 months old, the exponent 1.0 in Eq. [2] can give comparatively higher predicted values than the observed values. Therefore, the objective of this study was to replace exponent 1.0 by some other exponent that can improve the predictive performance of Eq. [2] for children ≤3 months old.

## Materials and methods

From the literature, the clearance values for 43 drugs (all small molecules or conventional drugs) were randomly selected for children between 0 and 1 year. The data were obtained through a PubMed search. There was no preconceived notion that a particular drug has to be included in the study. The children were divided into two groups: one group consisted of children between 0 and 3 months (90 observations) and the other group consisted of children between >3 months and 1 year (17 observations). This was done to evaluate if the proposed exponent 1.2 was suitable for the prediction of drug clearance in older children (>3 months). Owing to the paucity of data, some data were included in the second group of children where the age range was <3 months to 1 year. For example, the age range for fentanyl was 1–12 months. The chosen drugs are eliminated by extensive metabolism, exclusively by renal route or by both mechanisms (renal and hepatic). The following methods were used to predict clearance in the children and the predicted values were then compared with the observed values. When original body weights of the children were not available, an average body weight for that age group was used as described by Haddad et al. (17).

### Method I

The clearance in children was predicted according to Eq. [2] (exponent 0.75).

### Method II

The clearance in children was predicted according to Eq. [2] but exponent 0.75 was replaced by exponent 1.

### Method III

The clearance in children was predicted according to Eq. [2] but exponent 0.75 was replaced by 1.2. Exponent 1.2 was selected based on observations. For example, in one study (11) it was noted that the exponent of allometry was >1.0 in neonates and infants. An internal analysis with other drugs also indicated that the exponent of allometry was greater than 1.0 in neonates and infants. It should be noted, however, that in these studies the exponents of allometry widely varied and an exponent 1.2 was chosen as a middle ground and was deemed a suitable exponent to replace 0.75 or 1.0 in Eq. [2] for children ≤3 months.

### Statistical analysis

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

$$\%\text{error} = \frac{\sum(predicted - observed) * 100}{observed} \quad [3]$$

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

$$\text{mean square error (MSE)} = \frac{\sum (predicted - observed)^2}{n} \quad [4]$$

$$\text{RMSE} = (\text{MSE})^{0.5} \quad [5]$$

RMSE was expressed as percent of mean using Eq. [6]:

$$\%\text{RMSE} = \frac{(RMSE * 100)}{mean\ observed\ CL} \quad [6]$$

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

## Results

### Children ≤3 months

The predicted and observed clearance values and percent prediction error by all three methods in children (≤3 months) for 34 drugs (90 observations) are summarized in Table 1. The results of the study indicate that the exponent 0.75 provided the worst prediction of drug clearance, whereas exponent 1.2 was the best for children 3 months and younger. In children ≤3 months, there were 6, 27, and 32 observations for which the prediction error was ≤30% by exponent 0.75, 1.0, and 1.2, respectively. There were 12, 40, and 50 observations for which the prediction error was ≤50% by exponent 0.75, 1.0, and 1.2, respectively. The number of observations for which prediction error was ≥100% was 70, 32, and 12, by exponent 0.75, 1.0, and 1.2, respectively. There were 11, 4, and 0 observations with prediction error >1000% by 0.75, 1.0, and 1.2, respectively. The RMSE (Table 2) for exponent 0.75, 1.0, and 1.2 was 42.5, 15.3, and 12.1, respectively. Although, there was not much difference in the RMSE values between exponent 1.0 and 1.2, the superior prediction of drug clearance by exponent 1.2 was evident by a higher number of low prediction errors as compared to exponent 1.0 in children 3 months and younger. Out of 90 observations, there were 40 and 50 observations by exponent 1.0 and 1.2 for which prediction error was ≤50%, respectively.

### Children (>3 months and 1 year)

The predicted and observed clearance values and percent prediction error by all three methods in children (>3 months and 1 year) for 16 drugs (17 observations) are summarized in Table 3. The results of the analysis indicated that the application of exponent 1.0 (body weight normalized) in Eq. [2] was the best method to predict drug clearance in children for this age group (Table 3). Exponent 1.2 underestimated the clearance for all 17 observations in children >3 months to 1 year. The number of observations (out of 17) with ≤50% error for exponent 0.75, 1.0, and 1.2 were 8, 14, and 10, respectively (Table 4). The exponent 0.75 was also the worst approach for this age group. The RMSE for exponent 0.75, 1.0, and 1.2 was 35.7, 17.6, and 29.9, respectively (Table 4).

The current analysis further strengthens the previous observations of Mahmood (11, 16) that the exponent 0.75 is the worst approach for the prediction of drug clearance in neonates and infants. The approach produces unacceptable prediction error (in many cases over 1000% error) in very young children. By contrast, when exponent 1.0 was used on the body weight, the prediction of clearance was somewhat reasonable and far less erratic than 0.75 for children ≤1 year old. However, the prediction error was further reduced when exponent 1.2 was used for children ≤3 months old. Overall, out of 107 observations, there were 66 observations for which prediction error was ≤50% when exponent 1.0 and 1.2 (combined) were used for children between 0 and 1 year of age. By contrast, there were only 20 observations out of 107 observations for which prediction error was ≤50% when exponent 0.75 was used for this age group.

## Discussion

The pharmacokinetics and pharmacodynamics of a drug can differ between adults and children. These differences are mainly due to the physiological and biochemical differences among infants, children, adolescents, and adults. The ontogenesis of clearance mechanism can be the most critical determinant of a pharmacological response in infants and children (2, 3). Numerous articles have been published outlining the developmental changes in children and the need to predict drug clearance in children in order to select an optimal dose (3, 59). Several methods (2, 60, 61) have been suggested to predict the clearance in children from adult data and one of these methods is based on allometric size models (15). This model uses a fixed exponent of 0.75 based on Kleiber's (62) original work relating basal metabolic rate against body weight across several species. However, a systematic analysis by Mahmood (11, 16) indicated that the exponent 0.75 is not the best exponent for the prediction of drug clearance in children across all age groups. Exponent 0.75 performs reasonably well when children are over 5 years of age but its use in children ≤5 years should be avoided.

The exponents of clearance for a given drug are not universal and will vary depending on the species and sample size used in the allometric scaling (63). Owing to this very nature of the exponents of allometry, it is not surprising that one single exponent can neither be used for interspecies scaling (63, 64) nor for predicting drug clearance in children across all ages (11, 16).

Although there are many proponents (15, 65–68) of a fixed exponent of 0.75 for basal metabolic rate or drug clearance (these two terms are unrelated but many fail to recognize this difference), the investigative studies of many with experimental data suggest that the concept of exponent 0.75 is

**Table 1** Predicted and observed clearance (mL/min) in children ≤3 months.

| Drugs/age[a] | Observed CL (mL/min) | Predicted CL (0.75) | Predicted CL (1.0) | Predicted CL (1.2) | % Error (0.75) | % Error (1.0) | % Error (1.2) |
|---|---|---|---|---|---|---|---|
| Morphine (18) | | | | | | | |
| 24–41 weeks (GA) | 5.7 | 78 | 30 | 14 | 1276 | 426 | 144 |
| <1 week | 23 | 148 | 70 | 38 | 551 | 208 | 69 |
| 1 week–2 months | 35 | 161 | 78 | 44 | 357 | 122 | 25 |
| Fentanyl (19, 20) | | | | | | | |
| <2 days | 29 | 65 | 27 | 13 | 121 | –9 | –55 |
| 0.5–7 days | 44 | 77 | 33 | 17 | 74 | –24 | –61 |
| 1–71 days | 96 | 129 | 67 | 39 | 34 | –31 | –59 |
| 0.5–14 days | 38 | 84 | 37 | 20 | 120 | –2 | –48 |
| <1 month | 52 | 92 | 43 | 23 | 78 | –18 | –55 |
| Midazolam (21, 22) | | | | | | | |
| 1–7 days (PT) | 2.5 | 32 | 13 | 6.5 | 1184 | 428 | 159 |
| 1–7 days (term) | 5 | 44 | 20 | 10.5 | 770 | 296 | 111 |
| 34–41 weeks (GA) | 21 | 45 | 20 | 11.0 | 112 | –3 | –48 |
| Propofol (23) | | | | | | | |
| 4–25 days | 57 | 159 | 69 | 35 | 180 | 20 | –39 |
| Theophylline (3, 24) | | | | | | | |
| 1–7 days (PT) | 0.6 | 3.2 | 1.3 | 0.6 | 448 | 126 | 11 |
| 7–28 days (PT) | 1.5 | 4.3 | 2.0 | 1.0 | 183 | 29 | –32 |
| 1–7 days | 1.0 | 4.8 | 2.2 | 1.2 | 401 | 136 | 28 |
| 7–28 days | 1.6 | 5.9 | 3.0 | 1.7 | 275 | 90 | 9 |
| 3–15 days | 1.2 | 5.4 | 2.6 | 1.5 | 348 | 120 | 24 |
| 25–57 days | 3.8 | 7.3 | 4.0 | 2.4 | 92 | 4 | –37 |
| 1–3 months | 2.8 | 6.4 | 3.3 | 1.9 | 124 | 16 | –32 |
| Caffeine (3) | | | | | | | |
| 1–7 days (PT) | 0.2 | 6.8 | 2.8 | 1.4 | 3043 | 1192 | 535 |
| 7–28 days (PT) | 0.6 | 9.2 | 4.2 | 2.2 | 1438 | 600 | 273 |
| 1–3 months | 4.2 | 13.5 | 7.0 | 4.1 | 225 | 68 | –1 |
| Linezolid (25) | | | | | | | |
| Preterm <1 week | 4 | 8.3 | 3 | 1.7 | 107 | –15 | –58 |
| Full-term <1 week | 11 | 11.2 | 5 | 2.7 | –1 | –55 | –76 |
| >1 week <28 days | 20 | 13.9 | 7 | 3.8 | –32 | –67 | –81 |
| >28 days–<3 months | 30 | 17.7 | 9 | 5.6 | –40 | –68 | –81 |
| Vancomycin (3) | | | | | | | |
| 7–28 days (PT) | 3.3 | 8.8 | 4.0 | 2.1 | 163 | 20 | –36 |
| 1–7 days (term) | 2.5 | 8.8 | 4.0 | 2.1 | 250 | 60 | –15 |
| 7–28 days (term) | 3.8 | 10.9 | 5.3 | 3.0 | 183 | 39 | –22 |
| 1–3 months | 10.0 | 12.8 | 6.7 | 3.9 | 28 | –34 | –61 |
| Gentamicin (3) | | | | | | | |
| 1–7 days (PT) | 1.7 | 7.4 | 3.0 | 1.5 | 329 | 76 | –13 |
| 7–28 days (PT) | 5.2 | 10.0 | 4.5 | 2.4 | 94 | –12 | –53 |
| 1 day (term) | 3.0 | 10.0 | 4.5 | 2.4 | 236 | 53 | –18 |
| 1–7 days (term) | 4.1 | 10.0 | 4.5 | 2.4 | 142 | 10 | –41 |
| 7–28 days (term) | 7.3 | 12.4 | 6.0 | 3.4 | 70 | –17 | –53 |
| Furosemide (26, 27) | | | | | | | |
| 2–58 days (PT) | 0.15 | 7.9 | 2.9 | 1.3 | 5154 | 1851 | 783 |
| 1–18 days (term) | 0.48 | 12.4 | 5.3 | 2.7 | 2480 | 1014 | 469 |
| 3–32 days | 0.52 | 10.9 | 4.5 | 2.2 | 1997 | 767 | 328 |
| Methotrexate (28) | | | | | | | |
| 0–3 months | 17 | 18 | 9 | 4.8 | 3 | –50 | –72 |
| Amphotericin B (29) | | | | | | | |
| 17 days | 0.13 | 0.59 | 0.19 | 0.08 | 357 | 48 | –39 |
| Ertythromycin (30) | | | | | | | |
| 1.5 days | 33 | 47 | 21 | 11 | 42 | –35 | –66 |
| 15 days | 32 | 53 | 25 | 14 | 66 | –22 | –57 |
| 29 days | 39 | 58 | 29 | 16 | 50 | –26 | –59 |
| Cisapride (31) | | | | | | | |
| 31 days | 13 | 30 | 12 | 6 | 125 | –11 | –57 |
| 41 days | 37 | 44 | 20 | 11 | 19 | –46 | –71 |

(Table 1 continued)

| Drugs/age[a] | Observed CL (mL/min) | Predicted CL (0.75) | Predicted CL (1.0) | Predicted CL (1.2) | % Error (0.75) | % Error (1.0) | % Error (1.2) |
|---|---|---|---|---|---|---|---|
| Alfentanil (19) | | | | | | | |
| 27–36 weeks (GA) | 4.4 | 25 | 10 | 5 | 475 | 136 | 16 |
| 0–4 days | 5.3 | 30 | 13 | 7 | 464 | 145 | 26 |
| Ketamine (18) | | | | | | | |
| <3 months | 53 | 137 | 67 | 33 | 158 | 26 | –38 |
| Meropenem (32) | | | | | | | |
| 5–44 days | 3 | 12 | 4 | 2 | 314 | 47 | –36 |
| Moxalactam (33) | | | | | | | |
| 0–7 days | 1.2 | 4.9 | 1.9 | 0.9 | 312 | 55 | –29 |
| 0–7 days | 3.0 | 8.1 | 3.6 | 1.9 | 170 | 20 | –38 |
| 7–28 days | 3.0 | 8.8 | 4.0 | 2.1 | 192 | 33 | –29 |
| Cefoperazone (34) | | | | | | | |
| GA 33–36 weeks (PT) | 0.8 | 3.5 | 1.3 | 0.6 | 361 | 67 | –26 |
| GA 27–32 weeks (PT) | 2.0 | 7.1 | 3.3 | 1.8 | 257 | 64 | –12 |
| GA>37 weeks (term) | 3.5 | 7.8 | 3.7 | 2.0 | 124 | 6 | –42 |
| Pleconaril (35) | | | | | | | |
| 7–18 days | 91 | 44 | 21 | 12 | –52 | –77 | –87 |
| Zidovudine (36, 37) | | | | | | | |
| 5.5 days (PT) | 3.1 | 90 | 32.8 | 15 | 2810 | 959 | 372 |
| 17.7 days (PT) | 9 | 130 | 53.4 | 26 | 1376 | 507 | 198 |
| <14 days (term) | 31 | 167 | 74.8 | 39 | 439 | 141 | 27 |
| >14 days (term) | 61 | 185 | 85.4 | 46 | 203 | 40 | –24 |
| Fluconazole (38) | | | | | | | |
| 1 day | 0.16 | 0.76 | 0.26 | 0.1 | 377 | 61 | –33 |
| 7 days | 0.30 | 0.76 | 0.26 | 0.1 | 155 | –14 | –64 |
| 13 days | 0.52 | 0.83 | 0.29 | 0.1 | 59 | –45 | –77 |
| Isepmacin (39) | | | | | | | |
| 0–7 days | 2.2 | 6.8 | 2.8 | 1.4 | 210 | 27 | –37 |
| 0.6–2.9 months | 10.7 | 13.5 | 7.0 | 4.1 | 27 | –35 | –61 |
| Acetaminophen (40) | | | | | | | |
| 27–35 weeks GA | 3.8 | 22.9 | 9.4 | 4.6 | 502 | 147 | 21 |
| 37–40 weeks GA | 9.4 | 41.5 | 19.3 | 10.5 | 341 | 105 | 12 |
| <1 day | 7 | 27.0 | 11.8 | 6.0 | 286 | 68 | –14 |
| >10 days | 7.2 | 31.0 | 14.1 | 7.5 | 330 | 96 | 4 |
| Bupivacine (18) | | | | | | | |
| 1–21 days | 12 | 53.1 | 24.5 | 13.2 | 342 | 105 | 10 |
| Salbutamol (41) | | | | | | | |
| 54–105 days | 17 | 39.6 | 16.7 | 8.3 | 133 | –2 | –51 |
| Famotidine (42, 43) | | | | | | | |
| 0–3 months | 13 | 58.1 | 28.4 | 16.0 | 347 | 118 | 23 |
| 5–19 days | 15 | 85 | 47 | 29 | 467 | 213 | 93 |
| Indomethacin (3) | | | | | | | |
| 7–28 days | 0.42 | 9.2 | 4.2 | 2.2 | 2098 | 900 | 433 |
| Piperacillin (44) | | | | | | | |
| 29–31 weeks GA | 1.7 | 10.3 | 3.6 | 1.5 | 508 | 112 | –10 |
| 33–35 weeks GA | 4.5 | 20.5 | 9.0 | 4.6 | 356 | 100 | 2 |
| 38–42 weeks GA | 8.6 | 26.4 | 12.6 | 6.9 | 207 | 47 | –20 |
| Ceftazidime (45) | | | | | | | |
| Day 3 | 0.58 | 4.8 | 1.7 | 0.8 | 735 | 198 | 30 |
| Day 10 | 0.84 | 5.1 | 1.9 | 0.8 | 511 | 122 | –1 |
| Netilmicin (46) | | | | | | | |
| GA 23–28 weeks (PT) | 4.4 | 3.5 | 1.2 | 0.5 | –20 | –73 | –89 |
| GA 29–32 weeks (PT) | 6.8 | 4.0 | 1.4 | 0.6 | –41 | –79 | –91 |
| 2–16 days | 2.8 | 7.9 | 3.5 | 1.8 | 183 | 25 | –35 |
| Amoxicillin (47, 48) | | | | | | | |
| 29 weeks GA | 1.0 | 8.5 | 3.1 | 1.4 | 751 | 207 | 36 |
| 10–52 days | 6.81 | 13.9 | 5.9 | 3.0 | 104 | –13 | –56 |
| Ibuprofen (49) | | | | | | | |
| 22–31 weeks GA | 0.034 | 2.2 | 0.8 | 0.3 | 6449 | 2135 | 846 |

(Table 1 continued)

| Drugs/age[a] | Observed CL (mL/min) | Predicted CL (0.75) | Predicted CL (1.0) | Predicted CL (1.2) | % Error (0.75) | % Error (1.0) | % Error (1.2) |
|---|---|---|---|---|---|---|---|
| Meperidine (50) | | | | | | | |
| Preterm | 22.4 | 85.8 | 35.7 | 17.7 | 283 | 59 | –21 |
| Term <1 week | 29.4 | 125.8 | 59.5 | 32.7 | 328 | 102 | 11 |
| Term >3 weeks | 61.9 | 166.9 | 86.7 | 51.3 | 170 | 40 | –17 |
| Rifampicin (51) | | | | | | | |
| 11–55 days | 5.8 | 14.4 | 5.6 | 2.6 | 148 | 4 | 57 |

[a]Numbers in parenthesis are reference numbers. GA, gestational age; PT, preterm.

**Table 2** RMSE and the number of drugs within different categories of percent error in the prediction of clearance in neonates ≤3 months (n=90).

| Error | Exp 0.75 | Exp 1.0 | Exp 1.2 |
|---|---|---|---|
| % RMSE | 42.5 | 15.3 | 12.1 |
| % Error | | | |
| ≤30 | 6 | 27 | 32 |
| ≤50 | 12 | 40 | 50 |
| 51–99 | 8 | 18 | 28 |
| ≥100 | 70 | 32 | 12 |

theoretical and without any merit (64, 69–74). There is no place for any fixed exponent in allometric scaling because the exponents of allometry are data-dependent.

Although others reported that the exponent of basal metabolic rate and body mass is 0.75 in mature animals, it does not seem that this concept is true when animals at different stages of development are used (71, 75, 76). In humans, a study by Brody indicated different slopes for basal metabolism. For example, in males for ages 0–3 years, 3–16 years, 16–31 years, 31–60 years, and over 60 years, the exponents of basal metabolism were 1.02, 0.59, 0.65, 0.56, and 0.55, respectively. In females, for ages 0–3 years, 3–16 years, 16–31 years, 31–60 years, and over 60 years, the exponents of basal metabolism were 1.05, 0.64, 0.46, 0.38, and 0.57, respectively (75).

This view was also supported by Wieser (76) who also maintained that the rate of metabolism of a mammal changes during its development through various life stages. In each of these stages, the allometric exponent for metabolism is different than the other stages. For example, he mentions that the exponent for a growing fetus is similar to a maternal organ but there is a rapid increase in the exponent after birth. McMahon and Bonner (77) pointed out that a log-log plot of arm length against body height resulted in two slopes. The slope at the early stages of development is 1.2 and it is 1.0 at the later stages of development.

In light of above examples and considering that the slopes of basal metabolism vary during different stages of life, it is not logical to use a universal exponent across all age groups for the prediction of drug clearance in children. The current analysis further supports the views of Chappell and Mordenti, Wieser, and McMahon and Bonner.

In this study, although exponent 1.2 was found the most suitable exponent for the prediction of drug clearance in children ≤3 months old, there could be exceptions. For example, for morphine, exponent 1.2 was the best exponent for the prediction of drug clearance in all three age groups, yet for fentanyl, exponent 1.0 was found to be better than 1.2 in all five age groups. It is therefore practically impossible to select a best exponent for every drug. As a result, one has to rely on an exponent which performs reasonably well across most of the drugs. In this particular case, it seems that the exponent 1.2 performs better for most of the drugs than exponent 1.0 for the prediction of drug clearance in children ≤3 months old.

It should be noted that the methods II and III (exponent 1.0 and 1.2) as compared to method I (exponent 0.75) could help in reducing the prediction error but not necessarily provide an accurate prediction of drug clearance in children. For example, the prediction error in morphine clearance in children 24–41 weeks of gestational age was 1276%, 426%, and 144% by exponent 0.75, 1.0, and 1.2, respectively. Although, exponent 1.2 substantially improved the prediction of morphine clearance in the children (24–41 weeks of gestational age) as compared to exponent 0.75 or 1.0, yet the prediction error by exponent 1.2 was 144% which might not be acceptable in real life situations. Despite this uncertainty in the prediction of drug clearance in children, a given method could be more acceptable than other methods. For example, out of 90 observations in children ≤3 months, 78 observations (87%) had less than 100% prediction error by exponent 1.2, whereas 58 observations (67%) had less than 100% prediction error by exponent 1.0. The worst prediction was obtained by exponent 0.75; there were only 20 (23%) observations with less than 100% prediction error. Thus, uncertainty in the prediction of drug clearance in certain age groups of children does exist, yet a given method could prove to be more accurate than other method(s).

The current method adds to all other available methods which are attempts to predict drug clearance in children. It should be noted that none of the currently available methods (including the current proposed method) is perfect and will predict drug clearance in children with different degrees of accuracy and error. The prediction error by a particular method cannot be conceived a priori because a particular method can yield a good prediction for a given drug for a given age, yet that method could prove to be highly erratic for another drug for the same age group. Therefore, the suggested method

**Table 3** Predicted and observed clearance (mL/min) in children >3 months and ≤1 year.

| Drugs/age[a] | Observed CL (mL/min) | Predicted CL (0.75) | Predicted CL (1.0) | Predicted CL (1.2) | % Error (0.75) | % Error (1.0) | % Error (1.2) |
|---|---|---|---|---|---|---|---|
| Morphine (18) | | | | | | | |
| 2–6 months | 132 | 227 | 124 | 76 | 72 | –6 | –42 |
| Fentanyl (19, 20) | | | | | | | |
| 1–12 months | 107 | 79 | 146 | 48 | –27 | 36 | –55 |
| Caffeine (3) | | | | | | | |
| 3–12 months | 13.7 | 19.3 | 11.2 | 7.3 | 41 | –18 | –47 |
| Vancomycin (3) | | | | | | | |
| 3–12 months | 13.3 | 18.3 | 10.6 | 6.9 | 37 | –20 | –48 |
| Methotrexate (28) | | | | | | | |
| 6–12 months | 39 | 29 | 17 | 11.1 | –24 | –56 | –72 |
| 0–1 year | 71 | 27 | 15 | 9.5 | –62 | –79 | –87 |
| AmphotericinB (29) | | | | | | | |
| 1–8 months | 7.2 | 0.9 | 0.4 | 0.2 | –87 | –95 | –97 |
| Omeprazole (3) | | | | | | | |
| 0.25–1 year | 47 | 93 | 53 | 33 | 99 | 12 | –30 |
| Nizatidine (52) | | | | | | | |
| 0.46 year | 76 | 123 | 67 | 41 | 62 | –12 | –46 |
| Alfentanil (19) | | | | | | | |
| 0.3–0.9 year | 62 | 92 | 53 | 34 | 49 | –15 | –46 |
| Cefetamet (53) | | | | | | | |
| 3.5–11 months | 15 | 27 | 16 | 9 | 78 | 3 | –40 |
| Meropenem (54) | | | | | | | |
| 2–5 months | 17 | 33 | 16 | 9 | 92 | –6 | –47 |
| Cefepime (55) | | | | | | | |
| 2–6 months | 10 | 14 | 7 | 4 | 42 | –32 | –63 |
| Rapacuronium (56) | | | | | | | |
| 2–11 months | 50 | 94 | 54 | 35 | 88 | 8 | –30 |
| Famotidine (42, 43) | | | | | | | |
| >3–12 months | 50 | 83 | 46 | 28 | 66 | –9 | –43 |
| Ciprofloxacin (57) | | | | | | | |
| 3 months–1 year | 67 | 82 | 46 | 29 | 23 | –31 | –57 |
| Trovofloxacin (58) | | | | | | | |
| 4–12 months | 15 | 18 | 10 | 6 | 19 | –36 | –60 |

[a]Numbers in parenthesis are reference numbers.

**Table 4** RMSE and the number of drugs within different categories of percent error in the prediction of clearance in infants >3 months and ≤1 year (n=17).

| Error | Exp 0.75 | Exp 1.0 | Exp 1.2 |
|---|---|---|---|
| % RMSE | 35.7 | 17.6 | 26.9 |
| % Error | | | |
| ≤30 | 3 | 11 | 3 |
| ≥50 | 8 | 16 | 11 |
| 51–99 | 9 | 1 | 6 |
| ≥100 | 0 | 0 | 0 |

is not a substitute for a clinical trial in children and an accurate estimate of pharmacokinetic parameters in children for a drug can only be obtained by conducting a true pharmacokinetic study. However, the practical application and importance of allometry for the prediction of drug clearance in children cannot be ignored because predicted clearance values (although with some prediction error) can be very useful.

## Conclusions

The current analysis is an attempt to improve the prediction of drug clearance in children ≤1 year old. Although exponent 1.0 or body weight normalized clearance in children for this age group provides a very reasonable prediction of drug clearance, it appears that an improvement in the prediction of drug clearance in children ≤3 months can be obtained by a slight change in the approach. Therefore, I suggest the following for the prediction of drug clearance in children ≤1 year of age:

- If the age of the child is ≤3 months, then the exponent 1.2 should be used in Eq. [2].
- If the age of the child is >3 months and ≤1 year, then exponent 1.0 should be used in Eq. [2]. It must be recognized that application of 1.2 in Eq. [2] for children >3 months old could substantially underestimate predicted clearance as shown in Table 3.
- Exponent 0.75 should not be used at all for the aforementioned age groups as this approach will substantially overpredict the drug clearance.

- The suggested approach could be used to estimate a first-in-children dose in clinical trials based on the knowledge of observed adult clearance and predicted clearance in children. It should also be noted that in some instances exponent 1.2 in children ≤3 months underpredicted drug clearance. A better approach could be to obtain a range of drug clearance values in this age group by using both exponents (1.0 and 1.2) and then use the scientific judgment to select first-in-children dose.
- Although the current proposed method provides a reasonable degree of accurate prediction of drug clearance (which is a mean value within a given age group) in children, this approach might not be applicable for the prediction of drug clearance for an individual child in the age group reported in this study (1 year or less).

## Conflict of interest statement

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## References

1. Mahmood I. Dose selection in children: allometry and other methods. In: Pediatric pharmacology and pharmacokinetics. Rockville, MD: Pine House Publishers, 2005:184–216.
2. Alcorn J, McNamara PJ. Ontogeny of hepatic and renal systemic clearance pathways in infants: part I. Clin Pharmacokinet 2002;41:959–98.
3. Alcorn J, McNamara PJ. Ontogeny of hepatic and renal systemic clearance pathways in infants: part II. Clin Pharmacokinet 2002;41:1077–94.
4. Hayton WL. Maturation and growth of renal function: dosing renally cleared drugs in children. AAPS Pharm Sci 2000;2:1–7.
5. Hayton WL, Kneer J, de Groot R, Stoeckel K. Influence of maturation and growth on cefetamet pivoxil pharmacokinetics: rational dosing for infants. Antimicrob Agents Chemother 1996;40: 567–74.
6. Reigner BG, Blesch KS. Estimating the starting dose for entry into humans: principles and practice. Eur J Clin Pharmacol 2002;57:835–45.
7. Boxenbaum H, Dilea C. First-time-in-human dose selection: allometric thoughts and perspectives. J Clin Pharmacol 1995;35:957–66.
8. Collins JM, Zaharko S, Dedrick RL, Chabner BA. Potential roles for preclinical pharmacology in phase I clinical trials. Cancer Treat Rep 1986;70:73–80.
9. Mahmood I, Green MD, Fisher JE. Selection of the first time dose in humans: comparison of different approaches based on interspecies scaling of clearance. J Clin Pharmacol 2003;43: 692–7.
10. Mahmood I. First-in-human dose selection. In: Interspecies pharmacokinetic scaling: principles and application of allometric scaling. Rockville, MD: Pine House Publishers, 2005:259–87.
11. Mahmood I. Prediction of drug clearance in children: impact of allometric exponents, body weight, and age. Therap Drug Monitor 2007;29:271–8.
12. Mahmood I. Prediction of pharmacokinetic parameters in children: application of allometric principles. In: Pediatric pharmacology and pharmacokinetics. Rockville, MD: Pine House Publishers, 2005:142–83.
13. Schmidt-Nielsen K. Scaling: the size of living things. In: Why is animal size so important? Cambridge: Cambridge University Press, 1984:1–6.
14. Boxenbaum H. Interspecies pharmacokinetic scaling and the evolutionary comparative paradigm. Drug Metab Rev 1984;15:1071–121.
15. Holford NH. A size standard for pharmacokinetics. Clin Pharmacokinet 1996;30:329–32.
16. Mahmood I. Prediction of drug clearance in children from adults: a comparison of several allometric methods. Br J Clin Pharmacol 2006:61:545–57.
17. Haddad S, Restieri C, Krishnan K. Characterization of age-related changes in body weight and organ weights from birth to adolescence in humans. J Toxicol Environ Health A 2001;64:453–64.
18. Anderson BJ, McKee AD, Holford NH. Size, myths and the clinical pharmacokinetics of analgesia in paediatric patients. Clin Pharmacokinet 1997;33:313–27.
19. Jacqz-Aigrain E, Burtin P. Clinical pharmacokinetics of sedatives in neonates. Clin Pharmacokinet 1996;31:423–43.
20. Koehntop DE, Rodman JH, Brundage M, Hegland MG, Buckley JJ. Pharmacokinetics of fentanyl in neonates. Anesth Analg 1986;65:227–32.
21. Jacqz-Aigrain E, Wood C, Robieux I. Pharmacokinetics of midazolam in critically ill neonates. Eur J Clin Pharmacol 1990;39:191–2.
22. Peeters MY, Prins SA, Knibbe CA, Dejongh J, Mathôt RA, Warris C, et al. Pharmacokinetics and pharmacodynamics of midazolam and metabolites in non-ventilated infants after craniofacial surgery. Anesthesiology 2006;105:1135–46.
23. Allegaert K, de Hoon J, Verbesselt R, Naulaers G, Murat I. Maturational pharmacokinetics of single intravenous bolus of propofol. Paediatr Anaesth 2007;17:1028–34.
24. Theophylline package insert. www.accessdata.fda.gov/drugsatfda_docs/label/2009/019211s042lbl.pdf.
25. Jungbluth GL, Welshman IR, Hopkins NK. Linezolid pharmacokinetics in pediatric patients: an overview. Pediatr Infect Dis J 2003;22:S153–7.
26. Tuck S, Morselli P, Broquaire M, Vert P. Plasma and urinary kinetics of furosemide in newborn infants. J Pediatr 1983;103:481–5.
27. Vert P, Broquaire M, Legagneur M, Morselli PL. Pharmacokinetics of furosemide in neonates. Eur J Clin Pharmacol 1982;22:39–45.
28. Donelli MG, Zucchetti M, Robatto A, Perlangeli V, D'Incalci M, Masera G, et al. Pharmacokinetics of HD-MTX in infants, children, and adolescents with non-B acute lymphoblastic leukemia. Med Pediatr Oncol 1995;24:154–9.
29. Starke JR, Mason EO Jr, Kramer WG, Kaplan SL. Pharmacokinetics of amphotericin B in infants and children. J Infect Dis 1987;155:766–74.
30. Patamasucon P, Kaojarern S, Kusmiesz H, Nelson JD. Pharmacokinetics of erythromycin ethylsuccinate and estolate in infants under 4 months of age. Antimicrob Agents Chemother 1981;19:736–9.

31. Kearns GL, Robinson PK, Wilson JT, Wilson-Costello D, Knight GR, Ward RM, et al.; Pediatric Pharmacology Research Unit Network. Cisapride disposition in neonates and infants: in vivo reflection of cytochrome P450 3A4 ontogeny. Clin Pharmacol Ther 2003;74:312–25.
32. van Enk JG, Touw DJ, Lafeber HN. Pharmacokinetics of meropenem in preterm neonates. Ther Drug Monit 2001;23: 198–201.
33. Schaad UB, McCracken GH Jr, Threlkeld N, Thomas ML. Clinical evaluation of a new broad-spectrum oxa-beta-lactam antibiotic, moxalactam, in neonates and infants. J Pediatr 1981;98:129–36.
34. Rosenfeld WN, Evans HE, Batheja R, Jhaveri RC, Vohra K, Khan AJ. Pharmacokinetics of cefoperazone in full-term and premature neonates. Antimicrob Agents Chemother 1983;23: 866–9.
35. Kearns GL, Bradley JS, Jacobs RF, Capparelli EV, James LP, Johnson KM, et al.; Pediatric Pharmacology Research Unit Network. Single dose pharmacokinetics of pleconaril in neonates. Pediatr Infect Dis J 2000;19:833–9.
36. Boucher FD, Modlin JF, Weller S, Ruff A, Mirochnick M, Pelton S, et al. Phase I evaluation of zidovudine administered to infants exposed at birth to the human immunodeficiency virus. J Pediatr 1993;122:137–44.
37. Mirochnick M, Capparelli E, Dankner W, Sperling RS, van Dyke R, Spector SA. Zidovudine pharmacokinetics in premature infants exposed to human immunodeficiency virus. Antimicrob Agents Chemother 1998;42:808–12.
38. Saxén H, Hoppu K, Pohjavuori M. Pharmacokinetics of fluconazole in very low birth weight infants during the first two weeks of life. Clin Pharmacol Ther 1993;54:269–77.
39. Tod M, Padoin C, Petitjean O. Clinical pharmacokinetics and pharmacodynamics of isepamicin. Clin Pharmacokinet 2000;38:205–23.
40. Allegaert K, Van der Marel CD, Debeer A, Pluim MA, Van Lingen RA, Vanhole C, et al. Pharmacokinetics of single dose intravenous paracetamol in neonates: effect of gestational age. Arch Dis Child Fetal Neonatal Ed 2004;89:F25–8.
41. Kirpalani H, Koren G, Schmidt B, Tan Y, Santos R, Soldin S. Respiratory response and pharmacokinetics of intravenous salbutamol in infants with bronchopulmonary dysplasia. Crit Care Med 1990;18:1374–7.
42. Wenning LA, Murphy MG, James LP, Blumer JL, Marshall JD, Baier J, et al. Pharmacokinetics of famotidine in infants. Clin Pharmacokinet 2005;44:395–406.
43. James LP, Marotti T, Stowe CD, Farrar HC, Taylor BJ, Kearns GL. Pharmacokinetics and pharmacodynamics of famotidine in infants. J Clin Pharmacol 1998;38:1089–95.
44. Kacet N, Roussel-Delvallez M, Gremillet C, Dubos JP, Storme L, Lequien P. Pharmacokinetic study of piperacillin in newborns relating to gestational and postnatal age. Pediatr Infect Dis J 1992;11:365–9.
45. van den Anker JN, Hop WC, Schoemaker RC, van der Heijden BJ, Neijens HJ, de Groot R. Ceftazidime pharmacokinetics in preterm infants: effect of postnatal age and postnatal exposure to indomethacin. Br J Clin Pharmacol 1995;40:439–43.
46. Bergan T, Michalsen H. Pharmacokinetic assessment of netilmicin in newborns and older children. Infection 1982;10:153–8.
47. Pullen J, Driessen M, Stolk LM, Degraeuwe PL, van Tiel FH, Neef C, et al. Amoxicillin pharmacokinetics in (preterm) infants aged 10 to 52 days: effect of postnatal age. Ther Drug Monit 2007;29:376–80.
48. Huisman-de Boer JJ, van den Anker JN, Vogel M, Goessens WH, Schoemaker RC, de Groot R. Amoxicillin pharmacokinetics in preterm infants with gestational ages of less than 32 weeks. Antimicrob Agents Chemother 1995;39:431–4.
49. Aranda JV, Varvarigou A, Beharry K, Bansal R, Bardin C, Modanlou H, et al. Pharmacokinetics and protein binding of intravenous ibuprofen in the premature newborn infant. Acta Paediatr 1997;86:289–93.
50. Pokela ML, Olkkola KT, Koivisto M, Ryhänen P. Pharmacokinetics and pharmacodynamics of intravenous meperidine in neonates and infants. Clin Pharmacol Ther 1992;52:342–9.
51. Pullen J, Stolk LM, Degraeuwe PL, van Tiel FH, Neef C, Zimmermann LJ. Pharmacokinetics of intravenous rifampicin (rifampin) in neonates. Ther Drug Monit 2006;28:654–61.
52. Abdel-Rahman SM, Johnson FK, Connor JD, Staiano A, Dupont C, Tolia V, et al. Developmental pharmacokinetics and pharmacodynamics of nizatidine. J Pediatr Gastroenterol Nutr 2004;38:442–51.
53. Hayton WL, Walstad RA, Thurmann-Nielsen E, Kufaas T, Kneer J, Ambros RJ, et al. Pharmacokinetics of intravenous cefetamet and oral cefetamet pivoxil in children. Antimicrob Agents Chemother 1991;35:720–5.
54. Blumer JL, Reed MD, Kearns GL, Jacobs RF, Gooch WM 3rd, Yogev R, et al. Sequential, single-dose pharmacokinetic evaluation of meropenem in hospitalized infants and children. Antimicrob Agents Chemother 1995;39:1721–5.
55. Reed MD, Yamashita TS, Knupp CK, Veazey JM Jr, Blumer JL. Pharmacokinetics of intravenously and intramuscularly administered cefepime in infants and children. Antimicrob Agents Chemother 1997;41:1783–7.
56. Reynolds LM, Infosino A, Brown R, Hsu J, Fisher DM. Pharmacokinetics of rapacuronium in infants and children with intravenous and intramuscular administration. Anesthesiology 2000;92:376–86.
57. Lipman J, Gous AG, Mathivha LR, Tshukutsoane S, Scribante J, Hon H, et al. Ciprofloxacin pharmacokinetic profiles in paediatric sepsis: how much ciprofloxacin is enough? Intensive Care Med 2002;28:493–500.
58. Bradley JS, Kearns GL, Reed MD, Capparelli EV, Vincent J. Pharmacokinetics of a fluoronaphthyridone, trovafloxacin (CP 99,219), in infants and children following administration of a single intravenous dose of alatrofloxacin. Antimicrob Agents Chemother 2000;44:1195–9.
59. Kanamori M, Takahashi H, Echizen H. Developmental changes in the liver weight- and body weight-normalized clearance of theophylline, phenytoin and cyclosporine in children. Int J Clin Pharmacol Ther 2002;40:485–92.
60. Ginsberg G, Hattis D, Sonawane B. Incorporating pharmacokinetic differences between children and adults in assessing children's risks to environmental toxicants. Toxicol Appl Pharmacol 2004;198:164–83.
61. Ginsberg G, Hattis D, Russ A, Sonawane B. Physiologically based pharmacokinetic (PBPK) modeling of caffeine and theophylline in neonates and adults: implications for assessing children's risks from environmental agents. J Toxicol Environ Health A 2004;67:297–329.
62. Kleiber M. Body size and metabolism. Hilgardia 1932;6:315.
63. Mahmood I. Interspecies scaling of clearance. In: Interspecies pharmacokinetic scaling. Principles and application of allometric scaling. Rockville, MD: Pine House Publishers, 2005:39–85.
64. Mahmood I. Application of fixed exponent 0.75 to the prediction of human drug clearance: an inaccurate and misleading concept. Drug Metabol Drug Interact 2009;24:57–81.

65. West GB, Brown JH, Enquist BJ. A general model for the origin of allometric scaling laws in biology. Science 1997; 276:122–6.
66. West GB, Brown JH, Enquist BJ. The fourth dimension of life: fractal geometry and allometric scaling of organisms. Science 1999;284:1677–9.
67. Feldman HA, McMahon TA. The ¾ mass exponent for energy metabolism is not a statistical artifact? Respir Physiol 1983;52:149–63.
68. Savage VM, Gillooly JF, Woodruff WH, West GB, Allen AP. Enquist BJ, et al. The predominance of quarter-power scaling in biology. Funct Ecol 2004;18:257–82.
69. Petit G, Anfodillo T. Plant physiology in theory and practice: an analysis of the WBE model for vascular plants. J Theor Biol 2009;259:1–4.
70. Hayssen V, Lacy RC. Basal metabolic rates in mammals: toxonomic differences in the allometry of BMR and body mass. Comp Biochem Physiol 1985;81A:741–54.
71. Glazier DS. Beyond the '3/4-power law': variation in the intra- and interspecific scaling of metabolic rate in animals. Biol Rev Camb Philos Soc 2005;80:611–62.
72. Packard GC, Birchard GF. Traditional allometric analysis fails to provide a valid predictive model for mammalian metabolic rates. J Exp Biol 2008;211:3581–7.
73. Bokma F. Evidence against universal metabolic allometry. Funct Ecol 2004;18:184–7.
74. White CR, Cassey P, Blackburn TM. Allometric exponents do not support a universal metabolic allometry. Ecology 2007;88: 315–23.
75. Chappell WR, Mordenti J. Extrapolation of toxicological and pharmacological data from animals to humans. Adv Drug Res 1991;20:1–116.
76. Wieser W. A distinction must be made between the ontogeny and the phylogeny of metabolism in order to understand the mass exponent of energy metabolism. Respir Physiol 1984;55:1–9.
77. McMahon TA, Bonner JT. Proportions and size. In: On size and life. New York: Scientific American Library, 1983:25–67.