Prediction of Clearance in Children from Adults Following Drug–Drug Interaction Studies: Application of Age-Dependent Exponent Model

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Abstract
Background and Objective Pharmacokinetic drug–drug interaction (DDI) studies are conducted in adult subjects during drug development but there are limited studies that have characterized pharmacokinetic DDI studies in children. The objective of this study was to evaluate if the DDI clearance values from adults can be allometrically extrapolated from adults to children.

Methods Fifteen drugs were included in this study and the age of the children ranged from premature neonates to adolescents (30 observations across the age groups). The age-dependent exponent (ADE) model was used to predict the clearance of drugs in children from adults following DDI studies.

Results The prediction error of drug clearances following DDIs in children ranged from 4 to 67%. Of 30 observations, 17 (57%) and 27 (90%) observations had a prediction error ≤ 30% and ≤ 50%, respectively.

Conclusion This study indicates that it is possible to predict the clearance of drugs with reasonable accuracy in children from adults following DDI studies using an ADE model. The method is simple, robust, and reliable and can replace other complex empirical models.

1 Introduction
Drug interaction can lead to modification of a therapeutic response to a drug in an individual due to the exposure of the individual to one or more drugs or chemical substances. Drug interactions include drug–drug interaction (DDI), food–drug interaction, and chemical–drug interaction (for example, drug interaction with alcohol or tobacco) [1]. Drug interaction can alter the pharmacokinetics and/or pharmacodynamics of a drug. In pharmacokinetic drug interactions, the concentrations of one or more drugs are altered by another. This change in concentration in a given drug may be due to changes in absorption, distribution, metabolism, and elimination [1]. The pharmacodynamic interaction can lead to additive, synergistic, or antagonistic effects of a drug [1].

Like adults, children are also exposed to several drugs that may lead to DDIs; however, the magnitude of the drug interaction ratio (ratio with or without two drugs) may be age-dependent [2, 3].

Pharmacokinetic DDI studies are conducted in adults during drug development but there are limited studies that have characterized pharmacokinetic DDI studies in pediatrics [3]. Due to the difficulties in conducting a pediatric DDI PK study, a general and logical view may be that drug interaction studies may not be needed in children because one can extrapolate DDI information from adult data. This view may or may not be applicable to all drugs [3].

The metabolic enzymes and renal elimination mechanisms are quite immature during the early days of life [4–10]. Therefore, the rate and extent of drug metabolism and elimination of drugs are different in children (particularly neonates and infants) of different ages than adults. Similarly, the magnitude of DDIs may be different in neonates and infants than in children [3]. For example, in adults, an interaction can lead to a substantial increase in the clearance of one or both drugs but, due to immature metabolic enzymes, the clearance may be very different (marginal change or no change) in very young children, resulting in subtherapeutic or toxic effects if one tries to extrapolate the DDI information from adults to children. DDI studies in neonates, infants,
**Key Points**

Drug interaction can lead to modification of a therapeutic response to a drug in an individual due to the exposure of the individual to one or more drugs or chemical substances.

Pharmacokinetic drug–drug interaction (DDI) studies are conducted in adults during drug development but there are limited studies that have characterized pharmacokinetic DDI studies in children.

An allometric model (age-dependent exponent model) was used to predict DDI clearance in children (from preterm neonates to adolescents) using DDI adult clearance values following DDI studies.

This study indicated that it was possible to predict the clearance of drugs with reasonable accuracy (≤ 50% prediction error) in children from adults following drug–drug interaction studies using an age-dependent exponent model. The method is simple, robust, and reliable and can replace other complex empirical models.

and children are not regularly conducted, but one can find a limited number of such studies in the literature [3].

Drug interaction studies in children indicate that the direction of interaction may be similar to adults, but the magnitude of the interaction may be different [3]. Theoretically, in newborns and infants, one may see negligible or no interaction at all (due to the impact of ontogeny) or the magnitude of interaction may be very different than older children and adults.

The objective of this study was to evaluate if the drug clearance following a DDI can be allometrically extrapolated from adults to children.

## 2 Methods

From the literature, the clearance values of 15 randomly selected drugs were obtained for adults and children, using DDI studies [11–40]. Drugs were chosen when DDI studies were available in both adults and children. The allometric method used for the prediction of drug clearances in children was as follows.

The clearance of drugs with DDIs in children was predicted using an age-dependent exponent (ADE) model, which employs variable exponents as a function of age [41–45]. In this method, different allometric exponents were used for different age groups and the clearance of a drug was predicted in a given age group according to Eq. 1.

\[
\text{CL in children} = \text{adult CL with drug-drug interaction} \times \left(\frac{W_C}{W_{70}}\right)^b,
\]

where ‘adult clearance’ is the mean adult clearance of a given drug obtained from the literature, and CL in children is the predicted CL following DDIs (the same drugs as for adults); \(W_C\) is the weight of a child and \(W_{70}\) is the weight of an adult standardized to 70 kg.

Exponent ‘\(b\)’ in Eq. 1 is age-dependent. The exponents used in Eq. 1 were 1.2 for preterm neonates and 1.1 for term neonates aged 0–3 months, and 1.0, 0.9, and 0.75 for ages > 3 months–2 years, > 2–5 years, and > 5 years, respectively. The exponents selected in the ADE model [41–45, 49–55] are based on previous experience, observation, and data analysis (discussed later).

### 2.1 Statistical Analysis

The percentage prediction error between the observed and predicted clearance values was calculated according to the following equation:

\[
\% \text{error} = \frac{(\text{Predicted} - \text{observed}) \times 100}{\text{observed}}.
\]

The percentage prediction error of ≤ 30% or ≤ 50% was considered a reasonably accurate prediction.

## 3 Results

In this study, there were 15 drugs and 30 observations across the age groups (preterm to adolescents). The results of the study are shown in Tables 1 and 2. In Table 1, the observed clearance for adults and children with and without interaction ratios are shown. In addition, the data in Table 1 indicate that the interaction ratios between adults and children can be different.

In Table 2, the predicted and observed drug clearance values following DDIs in children are shown. The prediction error of drug clearances following DDIs in children ranged from 4 to 67%. Of 30 observations, only three drugs had a prediction error > 50%, with the highest being 67%, while 17 (57%) and 27 (90%) observations had prediction errors ≤ 30% and ≤ 50%, respectively.

Overall, when clearances of drugs were predicted in children following DDIs using adult clearance values following a DDI, a reasonably accurate prediction of clearance in children was noted.
| Drugs | Age, years | Observed alone | Observed interaction | Ratio[^a] | References |
|-------|------------|----------------|----------------------|-----------|------------|
| Theophylline-phenobarbital | | | | | |
| Theophylline | Adult | 52 ± 11 | 70 ± 23 | 1.35 | [11] |
| | Premature | 1.3 ± 0.4 | 1.5 ± 1.1 | 1.15 | [12] |
| | 6–12 | 40 ± 10 | 53 ± 23 | 1.33 | [13] |
| Zidovudine + dideoxyinosine | | | | | |
| Zidovudine | Adult | 3518 ± 1123 | 2505 ± 575 | 0.71 | [14] |
| | 3–14 | 1285 ± 224 | 1260 ± 515 | 0.98 | [15] |
| Dideoxyinosine + zidovudine | | | | | |
| Dideoxyinosine | Adult | 2660 ± 1297 | 2766 ± 686 | 1.04 | [14] |
| | 3–14 | 2488 ± 2100 | 2870 ± 1855 | 1.15 | [15] |
| Levetiracetam + inducers (carbamazepine, oxcarbazepine, phenobarbital, phenytoin) | | | | | |
| Levetiracetam | Adult | 97 ± 41 | 107 ± 49 | 1.10 | [16] |
| | 9.3 | 70 ± 29 | 100 ± 34 | 1.43 | [17] |
| Topiramate-carbamazepine | Adult | 33 ± 17 | 51 ± 11 | 1.55 | [18] |
| Topiramate | < 10 | 26 ± 11 | 42 ± 9 | 1.62 | [18] |
| Topiramate-phenobarbital | Topiramate | Adult | 33 ± 17 | 42 ± 11 | 1.27 | [18] |
| | Topiramate | < 10 | 26 ± 11 | 46 ± 19 | 1.77 | [18] |
| Topiramate | 0.9–1.84 | 8 ± 2 | 17 ± 2 | 2.13 | [19] |
| | 2–3.7 | 11 ± 3 | 18 ± 5 | 1.64 | [19, 20] |
| Lamotrigine + carbamazepine and phenytoin | Lamotrigine | Adult | 50 ± NA | 94 ± NA | 1.88 | [21] |
| | < 6 years | 13 ± 2 | 32 ± 11 | 2.46 | [22, 23] |
| | 7–14 | 19 ± 10 | 80 ± 27 | 4.21 | [22, 23] |
| Lamotrigine + valproic acid | Lamotrigine | Adult | 50 ± NA | 20 ± NA | 0.40 | [21] |
| | 0.8–2 | NA | 6.5 ± 3.8 | NA | [22] |
| | 6–14 | 19 ± 10 | 13 ± 16 | 0.69 | [22, 23] |
| Digoxin-carvedilol | Digoxin | Adult | 232 ± 39 | 201 ± 34 | 0.87 | [24] |
| | 0.08–7.7 | 35 ± 12 | 20 ± 3 | 0.57 | [25] |
| Artemether–nevirapine | Artemether | Adult | 10,019 ± NA | 33,057 ± NA | 3.30 | [26] |
| | 8.3 | 9526 ± NA | 10,103 ± NA | 1.06 | [27] |
| Lumifentraine lumefantrine | Adult | 27 ± NA | 35 ± NA | 1.30 | [26] |
| | 7.1 | 10 ± NA | 9 ± NA | 0.90 | [27] |
| Etoposide–cyclosporine | Etoposide | Adult | 40 ± 13 | 26 ± 14 | 0.65 | [28] |
| | 4.4–9.1 | 26 ± 6 | 14 ± 4 | 0.54 | [29] |
| | 12.1–17 | 27 ± 7 | 13 ± 4 | 0.48 | [29] |
| | 0.83–3.5 | NA | 7.4 ± NA | NA | [30] |
| | 14 | NA | 20 ± 6 | NA | [30] |
| Cyclosporine–grapefruit | Cyclosporine | Adult | 1131 ± 499 | 918 ± 378 | 0.81 | [31] |
| | 7–17 | 2034 ± 377 | 1232 ± 120 | 0.61 | [32] |
| Vecuronium–phenytoin | Vecuronium | Adult | 236 ± 27 | 561 ± NA | 2.38 | [33] |
| | 5–17 | 378 ± 151 | 589 ± 347 | 1.56 | [35] |
| Vecuronium–carbamazepine | Vecuronium | Adult | 266 ± 21 | 630 ± 84 | 2.37 | [33] |
| | 4–22 | 378 ± 151 | 808 ± 563 | 2.13 | [35] |
4 Discussion

Drug–drug interactions can be therapeutically beneficial or subtherapeutic, or can lead to toxicity. Therefore, DDI studies have become an integral part of modern-day drug development and drug therapy. DDI studies are rarely performed in children. Drug interaction studies are generally conducted in adults and it is then assumed that a similar observation will be noted across younger age groups. This may be true but the magnitude of interaction in terms of ratios of the area under the curve or clearance (with/without interaction) may differ from adults to children (Table 1). It is also possible that a DDI may not occur in adults or will be of very small magnitude, but in children the interaction may be of clinical significance (Table 1).

This study is an attempt to predict the clearance of drugs in children following DDI studies. The adult clearance values used in this study were obtained following DDI studies, and the approach is based on an ADE model proposed by Mahmood et al. [41–45]. The predictive performance of this method was previously validated in several studies by external data and was found to be reliable (prediction error ≤ 50% or ≤ 30%) [41–45]. In a recent study [45], the ADE model was compared with a physiologically based pharmacokinetic (PBPK) model and it was found that the predictive performance of both the ADE and PBPK models was comparable. The ADE model can be used from preterm neonates to adolescents based on fixed but variable age-dependent exponents. A recent publication with extensive data [46] further supported the previous observations [41–45] that the prediction of drug clearance from PBPK and ADE models is comparable across age groups. Other investigators [47, 48] also found that the ADE model is comparable with the PBPK model.

It should be noted that the allometric exponents are data-dependent and are not fixed in nature. Depending on the availability of the data, allometric exponents should be determined (if allometry is applicable to the data). For example, in interspecies scaling, three to four species are enough to determine the exponents of the allometry. There are however situations where allometric exponents cannot be determined because only one species is available. When only one species is available, there is no choice but to use theoretical fixed exponents. The theoretical exponents generally used are 0.75 for clearance and 1.0 for volume of distribution.

The concept of variable but fixed allometric exponents across the age groups is an integral part of the ADE model. For example, when one is extrapolating clearance from adults to preterm neonates, there are no data to determine the allometric exponent for a given age group; hence, a fixed exponent is used in the ADE model. This method has been well-tested and the results are satisfactory [41–45] and comparable with other methods [42, 44–48].

It is a well-known fact that the clearance of a good majority of drugs across the age groups (neonates to adults) can be described allometrically (since the body weight range is wide) and the exponents of allometry will depend on the weight range and clearance values. In most cases, a single allometric exponent cannot describe clearance versus weight data across the entire age groups (preterm neonates to adults). Under such circumstances, two to three allometric exponents may be needed to accurately describe clearance versus weight data across age groups [42, 49–51].

The exponents of the ADE model are based on the observations of many authors of past publications [52–55], as well as body weight-dependent exponent (BDE) models [49–51]. The ADE model is simple compared with other

| Drugs                        | Age, years | Observed alone | Observed interaction | Ratioa | References |
|------------------------------|------------|----------------|----------------------|--------|------------|
| Mycophenolate mofetil–tacrolimus (IV) |            |                |                      |        |            |
| Mycophenolate mofetil        | > 12 to 16 | NA             | 880 ± 360            | NA     | [36]       |
|                              | < 6        | NA             | 550 ± 197            | NA     | [36]       |
|                              | 6–12       | NA             | 725 ± 335            | NA     | [36]       |
| Mycophenolate mofetil–cyclosporine |            |                |                      |        |            |
| Mycophenolate mofetil        | Adult      | NA             | 181 ± 60             | NA     | [37]       |
|                              | 5–16       | NA             | 121 ± 36             | NA     | [37]       |
| Rifabutin–lopinavir/ritonavir |            |                |                      |        |            |
| Rifabutin                    | Adult      | NA             | 726 ± NA             | NA     | [38]       |
|                              | 0.8–1.75   | NA             | 109 ± 9              | NA     | [39]       |
| Sirolimus–cyclosporine       |            |                |                      |        |            |
| Sirolimus                    | Adult      | NA             | 162 ± 73             | NA     | [40]       |
|                              | 6–11       | NA             | 96 ± 58              | NA     | [40]       |
|                              | 12–18      | NA             | 118 ± 49             | NA     | [40]       |

NA not available, IV intravenous

a Ratio = with/without interaction
Table 2 Predicted and observed clearance (mL/min) following drug–drug interactions in children

| Age (years) | Weight (kg) | Observed CL | Predicted CL | Percentage error |
|-------------|-------------|-------------|--------------|------------------|
| Premature   | 2.5 (n=24)  | 1.5 ± 1.1   | 1.3          | − 14             |
| 6–12        | 32 (n=7)    | 53 ± 23     | 38           | − 29             |
| 3–14        | 35 (n=8)    | 1260 ± 515  | 1489         | 18               |
| 3–14        | 35 (n=8)    | 2870 ± 1855 | 1645         | 43               |

Levetiracetam + inducers (carbamazepine, oxcarbazepine, phenobarbital, phenytoin)

Adult CL = 107 ± 49 mL/min (effect on levetiracetam)

| Age (years) | Weight (kg) | Observed CL | Predicted CL | Percentage error |
|-------------|-------------|-------------|--------------|------------------|
| < 10        | 30 (n=4)    | 42 ± 9      | 27           | − 36             |

Topiramate-carbamazepine (effect on topiramate); adult CL = 51 ± 11 mL/min

| Age (years) | Weight (kg) | Observed CL | Predicted CL | Percentage error |
|-------------|-------------|-------------|--------------|------------------|
| < 10        | 30 (n=7)    | 46 ± 19     | 22           | − 52             |
| 0.9–1.84    | 13 (n=3)    | 17 ± 2      | 8            | − 54             |
| 2.3–7.7     | 16 (n=7)    | 18 ± 5      | 10           | − 47             |

Lamotrigine + carbamazepine and phenytoin (effect on lamotrigine)

Adult CL of lamotrigine with carbamazepine = 70 ± NA mL/min; with phenytoin = 118 ± NA mL/min

| Age (years) | Weight (kg) | Observed CL | Predicted CL | Percentage error |
|-------------|-------------|-------------|--------------|------------------|
| < 6         | 15 (n=3)    | 31 ± 11     | 22           | − 29             |
| 7–14        | 37 (n=4)    | 80 ± 27     | 58           | − 28             |

Digoxin-carvedilol (effect on digoxin); adult CL = 201 ± 34 mL/min

| Age (years) | Weight (kg) | Observed CL | Predicted CL | Percentage error |
|-------------|-------------|-------------|--------------|------------------|
| 0.8–7.7     | 8 (n=8)     | 20 ± 3      | 23           | 15               |

Lumefantrine (effect on lumefantrine); adult CL = 35 ± NA mL/min

| Age (years) | Weight (kg) | Observed CL | Predicted CL | Percentage error |
|-------------|-------------|-------------|--------------|------------------|
| < 6         | 18 (n=15)   | 9 ± NA      | 15           | 67               |

Etoposide–cyclosporine (effect on etoposide); adult CL = 25 ± 14 mL/min

| Age (years) | Weight (kg) | Observed CL | Predicted CL | Percentage error |
|-------------|-------------|-------------|--------------|------------------|
| 4.4–9.1     | 40 (n=6)    | 13 ± 4      | 16 ± 5       | 23               |
| 12.1–17     | 50 (n=6)    | 16 ± 7      | 19 ± 7       | 19               |
| 0.83–3.5    | 11 (n=2)    | 7.4         | 4.7          | 36               |
| 14          | 55 (n=3)    | 20 ± 6      | 21           | 4                |

Cyclosporine–grapefruit (effect on cyclosporine); adult CL = 985 ± 378 mL/min

| Age (years) | Weight (kg) | Observed CL | Predicted CL | Percentage error |
|-------------|-------------|-------------|--------------|------------------|
| 7–17        | 44 (n=6)    | 1227 ± 120  | 695          | − 43             |

Vecuronium–phenytoin (effect on vecuronium); adult CL = 561 ± NA mL/min

| Age (years) | Weight (kg) | Observed CL | Predicted CL | Percentage error |
|-------------|-------------|-------------|--------------|------------------|
| 5–17        | 39 (n=10)   | 589 ± 347   | 362          | − 39             |

Vecuronium–carbamazepine (effect on vecuronium); adult CL = 630 ± 84 mL/min

| Age (years) | Weight (kg) | Observed CL | Predicted CL | Percentage error |
|-------------|-------------|-------------|--------------|------------------|
| 4–22        | 43 (n=10)   | 808 ± 563   | 437          | − 46             |

Mycophenolate mofetil–tacrolimus (IV) [effect on mycophenolate]

From a clearance value of 880 ± 360 mL/min from adolescents > 12 to 16 years of age (weight = 60 kg)

| Age (years) | Weight (kg) | Observed CL | Predicted CL | Percentage error |
|-------------|-------------|-------------|--------------|------------------|
| < 6        | 20 (n=9)    | 550 ± 197   | 386          | − 30             |
| 6–12       | 30 (n=5)    | 725 ± 335   | 523          | − 28             |

Mycophenolate mofetil–cyclosporine (effect on mycophenolate); adult CL = 181 ± 60 mL/min

| Age (years) | Weight (kg) | Observed CL | Predicted CL | Percentage error |
|-------------|-------------|-------------|--------------|------------------|
| 5–16       | 50 (n=0)    | 121 ± 36    | 141          | 16               |

Rifabutin–lopinavir/ritonavir (effect on rifabutin); adult CL = 726 ± NA mL/min

| Age (years) | Weight (kg) | Observed CL | Predicted CL | Percentage error |
|-------------|-------------|-------------|--------------|------------------|
| 0.83–1.75   | 9 (n=3)     | 109 ± 9     | 93           | − 15             |
| 2.42–3.42   | 12 (n=3)    | 188 ± 87    | 138          | − 27             |

Sirolimus–cyclosporine (effect on sirolimus); adult CL = 162 ± 73 mL/min

| Age (years) | Weight (kg) | Observed CL | Predicted CL | Percentage error |
|-------------|-------------|-------------|--------------|------------------|
| 6–11        | 27 (n=8)    | 96 ± 58     | 79           | − 18             |
| 12–18       | 52 (n=14)   | 118 ± 49    | 130          | 10               |

Adult body weight normalized to 70 kg. If the body weights of children were not provided in the article, then the weights were estimated from the body weight chart of the Centers for Disease Control and Prevention (CDC) and from the literature

CL clearance, NA not available, IV intravenous
models (statistical empirical models as well as PBPK empirical models) and can be used in pediatric drug development to select first-in-children dose [41–45].

The metabolic enzymes and renal elimination mechanisms are quite immature during the early days of life. Therefore, the rate and extent of drug metabolism and elimination of drugs are different in children (particularly in neonates and infants) than adults. Similarly, the magnitude of DDI s may be different in neonates and infants than children. For example, in adults, an interaction can lead to a substantial increase in the clearance of one or both drugs, but, due to immature metabolic enzymes, the clearance may be very different (marginal change or no change at all) in very young children, especially preterm and term neonates. Therefore, in neonates and infants, extrapolation of a PK parameter from adult data can lead to serious prediction errors. Due to the paucity of DDI data in neonates and infants, a comprehensive analysis could not be performed in this study.

5 Conclusion

This study indicates that it is possible to predict the clearance of drugs with reasonable accuracy in children following DDI studies using an ADE model; however, there are many physiological and physical factors that may be hurdles for the prediction of drug clearance in children following DDI studies, but a reasonably accurate estimate of clearance is possible in children across the age groups using the proposed ADE model. It should be noted that the proposed method is not in lieu of a clinical trial, rather the methods should be used for the selection of first-in-children dose before initiating a pediatric DDI clinical trial. The proposed method is simple, robust, and reliable and can replace other complex empirical models. In an era of ‘fit for purpose’, simple models, if providing similar results, should be preferred over complex models that require too many covariates or too many and needless physiological parameters.

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Compliance with Ethical Standards

Conflict of interest Iftekhar Mahmood declares that he has no conflicts of interest.

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