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Prediction of drug clearance in children from adults: a comparison of several allometric methods

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Aims
In recent years with the advent of paediatric exclusivity and requirements to conduct clinical studies in children, the current emphasis is to find a safe and efficacious dose of a drug in children. It has been suggested that one can predict the clearance of a drug in children according to the equation: CL in the child = adult CL × (weight of the child/70)$^{0.75}$. Considering the controversy surrounding the exponent of 0.75 for the prediction of clearance and lack of any systematic evaluation of the aforementioned proposal, the objectives of the study were as follows: (i) to determine if indeed the exponent 0.75 is the most suitable exponent for the prediction of clearance in children from adult data; (ii) to explore and search for other exponents that are more accurate or as good as 0.75; and (iii) to propose a new approach (if any) based on the findings of the current evaluation.

Methods
Six methods were used to predict clearance of drugs in children from adult data. Besides evaluating the exponent of 0.75, exponents of 0.80, 0.85 and 1.0 were also evaluated. An empirical approach based on kidney and liver weights was also examined. Based on the results of five methods, a sixth method was introduced.

Results
The results of the study indicate that no single method is suitable for all drugs or for all age groups. The exponents 0.75, 0.80, and 0.85 provided the same degree of accuracy or error in the prediction of clearance in children.

Conclusions
Since no single method is suitable for all drugs or for all age groups. A combination of approaches is suggested which may help in improving the prediction of clearance in children from adult data.

Introduction

It is now well recognized that age, gender, disease and ethnic background can alter the pharmacokinetics and pharmacodynamics of a drug. In recent years with the advent of paediatric exclusivity and requirements to conduct clinical studies in children, there has been greater emphasis on evaluating the pharmacokinetics of drugs in children. Furthermore, dosing of drugs in chil-

dren requires a thorough consideration as there are physiological differences between children and adults. The variation in body composition and the differences in the functions of the liver and the kidneys between children and adults are considered to be the main sources of pharmacokinetic differences between these two groups. In neonates and infants, physiological events occur so rapidly that reasonably accurate prediction of drug clearance, and hence the required dosage regimen, in this population becomes very difficult [1]. Therefore, the current emphasis is to find a safe and efficacious dose of a drug in children based on the pharmacokinetic knowledge of a drug in adults.

Over the years, several approaches to determining paediatric doses have been suggested such as Young's rule or Clark's rule. The use of body surface area or body weight on a per kilogram basis is a common practice to dose children [2]. However, normalization of clearance for metabolically eliminated drugs, based on per kilogram body weight, has led to a false notion that children have a higher metabolic capacity than adults because of their relatively large liver size or increased liver blood flow [2]. Anderson *et al.* [2] have provided a good review of size and related myths with respect to the clinical pharmacokinetics of analgesics in children.

The simple allometric relationship has been shown to relate body size to a parameter of interest in the field of physiology, ecology, palaeontology and pharmacokinetics [3, 4]. These relationships are related to a power function or an exponent which can be as diverse as the aforementioned fields:

$$Y = aW^b \quad (1)$$

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

Equation 1 has been extensively used to predict pharmacokinetic parameters such as clearance, volume of distribution and half-life from laboratory animals to humans. According to Anderson *et al.* [2], the allometric principles can also be applied to predict drug clearance in children. Based on the suggestions of 'a size standard' [3], one can predict clearance of a drug in children according to the following equation:

$$\text{CL in the child} = \text{adult CL} \times (\text{weight of the child}/70)^{0.75} \quad (2)$$

where 70 kg is the standard weight of an adult and adult clearance can be normalized based on 70 kg adult body weight.

In 1932, Kleiber [4] investigated the basal metabolic rates in several species ($n = 13$) whose weight range was 3.7. Kleiber concluded that the basal metabolic rates of species are related to body size with an exponent of 0.734 (later rounded to 0.75 for the ease of calculation). In later years, this theory led to a misconception that the clearance of drugs can be extrapolated across species with an exponent of 0.75 and Kleiber's exponent of 0.75 became a classic standard and any argument against it was discarded.

The exponent of 0.75 for clearance has been widely debated [5]. Logically, it is difficult to perceive that the exponent of allometry for a given parameter will revolve around a fixed number. Over the years, many investigators have shown that the exponent of 0.75 is not necessarily the best scaling exponent for clearance [6–10]. It must be recognized that the number of species and the conditions under which a study is designed are the detrimental factors for the exponent of allometric scaling [8, 10].

Considering the controversy surrounding the exponent of 0.75 for the prediction of clearance and lack of any systematic evaluation of the aforementioned proposal, the objectives of the study were as follows:

- To determine if indeed the exponent of 0.75 is the most suitable exponent for the prediction of clearance in children from adult data.
- To explore and search for other exponents that are more accurate or as good as 0.75.
- To propose a new approach (if any) based on the findings of the current evaluation.

Methods

From the literature, the clearance values for 41 drugs (124 observations in children of different age groups) for children and adults were randomly selected. The age groups of the children varied widely. The clearance data included infants, children and adolescents with ages ranging from 1 day to 17 years. The chosen drugs are eliminated by extensive metabolism, exclusively by the 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 in that age group.

Method I The clearance in children was predicted according to equation 2. When children's original body weights were not available, an average body weight for that age group was used, as described by Haddad *et al.* [11].

Methods II–IV These three methods followed the same pattern as method I except that the exponents used were

Table 1
Predicted and observed clearance (l h^{-1}) in children using different methods

Drugs/age	Body weight (kg)	Obs CL (l h^{-1})	Pred CL (0.75)	Pred CL (0.8)	Pred CL (0.85)	Pred CL (1.0)	Pred CL L + K	Pred CL (mixed)
Morphine								
<1 week	3.5	1.365	6.513	5.607	4.827	3.080	3.560	3.080
1 week to 2 months	3.9	2.106	7.064	6.114	5.292	3.432	3.903	3.432
2–6 months	6.2	7.936	10.001	8.860	7.848	5.456	6.657	5.456
0.5–2.5 years	7.2	9.360	11.188	9.985	8.912	6.336	7.559	7.559
Adult	70	61.600						
Fentanyl								
<1month	3.2	3.104	5.536	4.745	4.067	2.560	2.999	2.560
1–12 months	5.9	6.431	8.760	7.741	6.840	4.720	5.802	4.720
1–5 years	17.3	11.937	19.629	18.304	17.068	13.840	16.650	16.650
Adult	70	56.000						
Remifentanil								
2–12 years	18	63.360	62.435	58.336	54.506	44.460	53.171	62.435
Adult	70	172.900						
Bupivacine								
1–21 days	3.2	0.704	3.183	2.728	2.338	1.472	1.725	1.472
5.5–10 years	23	13.800	13.974	13.218	12.502	10.580	12.197	13.974
Adult	70	32.200						
Ketamine								
<3 months	4	3.200	9.817	8.508	7.374	4.800	5.438	4.800
3–12 months	8	16.800	16.511	14.814	13.291	9.600	11.274	9.600
4 years	15	22.500	26.456	24.495	22.679	18.000	22.123	22.123
Adult	70	84.000						
Midazolam								
1–7 days (premature)	2	0.149	1.925	1.611	1.349	0.791	0.995	0.791
1–7 days term	3	0.300	2.609	2.229	1.904	1.187	1.404	1.187
34–41 weeks (gestational)	3.1	1.264	2.674	2.288	1.958	1.227	1.444	1.227
Mean 5.2 years	17.3	9.460	9.709	9.054	8.443	6.846	8.236	9.709
Adult	70	27.700						
Atenolol								
5–16 years	20	3.310	3.283	3.083	2.896	2.400	2.825	3.283
Adult	70	8.400						
Salbutamol								
54–105 days	2.2	1.000	2.374	1.997	1.679	0.999	1.239	1.000
Adult	70	31.800						

0.80, 0.85 and 1.0. The exponent 0.85 was selected as a compromise value for the allometric exponents of kidneys (0.820), liver (0.86) and liver blood flow (0.890). The exponent 0.80 was chosen as a central value between 0.75 and 0.85 and exponent 1.0 was used to evaluate if indeed there is any need for an exponent on the weight.

Method V An empirical approach was developed by using the liver and kidney weights of several species. The allometric scaling for the liver and kidney weights was performed across species (mouse, rat, rabbit, dog, monkey and human) against their respective body weights. The following allometric equations were generated for the prediction of liver and kidney weights in children using their body weight:

$$\text{Liver weight} = 40.7 \times (\text{body weight})^{0.86} \quad (3)$$

$$\text{Kidney weight} = 7.2 \times (\text{body weight})^{0.84} \quad (4)$$

The predicted liver and kidney weights were divided by the total liver and kidney weights of an adult (1800 g for the liver and 310 g for the kidneys). The mean of this ratio (equation 5) was then multiplied by the adult clearance to predict clearance in the children.

Table 1a
Predicted and observed clearance (l h^{-1}) in children using different methods

Drugs/age	Body weight (kg)	Obs CL (l h^{-1})	Pred CL (0.75)	Pred CL (0.8)	Pred CL (0.85)	Pred CL (1.0)	Pred CL L + K	Pred CL (mixed)
Rapacuronium								
2–11 months	7.7	3.000	5.635	5.046	4.519	3.245	3.833	3.245
1–3 years	13	4.100	8.346	7.672	7.052	5.479	6.879	6.879
Adult	70	29.500						
Topiramate								
<10 years	14.2	0.660	0.602	0.555	0.513	0.404	0.500	0.602
10–17 years	37.3	1.100	1.241	1.203	1.165	1.060	1.137	1.241
Adult	70	1.990						
With enzyme ind								
<10 years	14.2	1.210	0.976	0.901	0.832	0.655	0.812	0.976
10–17 years	37.3	2.350	2.014	1.952	1.892	1.721	1.845	2.014
Adult	70	3.230						
Theophylline								
1–7 days (premature)	2	0.035	0.190	0.159	0.133	0.078	0.098	0.078
7–28 days (premature)	3	0.092	0.257	0.220	0.188	0.117	0.138	0.117
1–7 days	3.4	0.057	0.282	0.243	0.209	0.133	0.154	0.133
7–28 days	4.5	0.094	0.349	0.304	0.265	0.176	0.195	0.176
1–3 months	5	0.170	0.377	0.331	0.290	0.195	0.214	0.195
2–5 years	14.5	1.030	0.838	0.775	0.716	0.566	0.699	0.699
6.5–12 years	24.2	1.490	1.231	1.167	1.107	0.944	1.080	1.231
Adult	70	2.730						
Antipyrine								
<12 years	18	1.040	0.896	0.837	0.782	0.638	0.763	0.896
>12 years	30	1.330	1.314	1.259	1.207	1.063	1.177	1.314
Adult	70	2.480						
Lorazepam								
<1 year	3	0.042	0.403	0.344	0.294	0.183	0.217	0.183
2–12 years	18	1.370	1.546	1.444	1.349	1.101	1.316	1.546
>12–18 years	30	1.850	2.267	2.173	2.083	1.834	2.032	2.267
Adult	70	4.280						
Famotidine								
0–3 months	4	0.800	3.483	3.018	2.616	1.703	1.929	1.703
>3–12 months	6.5	3.000	5.013	4.451	3.952	2.767	3.352	2.767
1.1–12.9 years	20	8.400	11.646	10.939	10.274	8.514	10.023	10.023
Adult	70	29.800						
Levofloxacin								
IV 0.5 to <2 years	9.4	3.290	2.329	2.107	1.906	1.410	1.616	1.616
2 to <5 years	13.7	4.384	3.090	2.848	2.625	2.055	2.560	2.560
5 to <10 years	24.9	6.225	4.836	4.593	4.361	3.735	4.255	4.836
10 to <12 years	45.1	8.569	7.551	7.387	7.226	6.765	7.050	7.551
12–16 years	57.5	10.350	9.060	8.971	8.883	8.625	8.668	9.060
Adult	70	10.500						

$$\text{Ratio} = [40.7 \times (\text{body weight})^{0.86}/1800 + 7.2 \times (\text{body weight})^{0.84}/310]/2 \quad (5)$$

Although the routes of elimination for the drugs were well known in adults, it was assumed that in children, especially in the very young, both the kidneys and the liver are functional simultaneously for the elimination of drugs. A correction factor of 1.15 was applied to the predicted clearance in the children. For children under 5 kg body weight the predicted clearance was divided by 1.15, and for children >10 kg the predicted clearance was multiplied by 1.15. No correction factor was applied between body weight >5 and 10 kg. The reason for

Table 1b
Predicted and observed clearance (l h^{-1}) in children using different methods

Drugs/age	Body weight (kg)	Obs CL (l h^{-1})	Pred CL (0.75)	Pred CL (0.8)	Pred CL (0.85)	Pred CL (1.0)	Pred CL L + K	Pred CL (mixed)
Lamotrigine								
<6 years	15	0.740	0.728	0.674	0.624	0.495	0.608	0.728
>6 years (3.8–11.3 years)	35	1.160	1.374	1.327	1.282	1.155	1.250	1.374
Adult	70	2.310						
Amprenavir								
4–12 years	26.67	31.740	23.520	22.412	21.356	18.479	20.835	23.520
Adult	70	48.500						
Gatifloxacin								
0.5–2 years	10	3.100	2.993	2.715	2.464	1.840	2.090	2.090
2–6 years	17	6.290	4.456	4.151	3.868	3.128	3.773	4.456
6–12 years	30	9.040	6.822	6.539	6.268	5.520	6.115	6.822
12–16 years	48	11.170	9.706	9.524	9.346	8.832	9.119	9.706
Adult	70	12.880						
Caffeine								
1–7 days (premature)	2	0.013	0.409	0.342	0.286	0.168	0.211	0.168
7–28 days (premature)	3	0.036	0.554	0.473	0.404	0.252	0.298	0.252
1–3 months	5	0.250	0.812	0.712	0.624	0.420	0.460	0.420
3–12 months	8	0.820	1.156	1.037	0.930	0.672	0.789	0.672
Adult	70	5.880						
Vancomycin								
7–28 days (premature)	3	0.200	0.527	0.450	0.384	0.240	0.283	0.240
1–7 days (term)	3	0.150	0.527	0.450	0.384	0.240	0.283	0.240
7–28 days (term)	4	0.230	0.653	0.566	0.491	0.319	0.362	0.319
1–3 months	5	0.600	0.772	0.677	0.593	0.399	0.438	0.399
3–12 months	8	0.800	1.099	0.986	0.885	0.639	0.750	0.639
Adult	70	5.590						
Cefetamet								
IV 3–5 years	15.8	2.830	2.574	2.389	2.218	1.774	2.164	2.164
5.5–12 years	30.8	4.360	4.246	4.076	3.912	3.458	3.816	4.246
Adult	70	7.860						
Chloramphenicol								
Premature	2	0.210	1.049	0.878	0.735	0.431	0.542	0.431
Infant	5	0.760	2.086	1.828	1.602	1.079	1.182	1.182
Child	20	1.900	5.901	5.543	5.206	4.314	5.079	5.079
Adult	70	15.100						
Valproic acid								
0–2 months	5	0.072	0.140	0.122	0.107	0.072	0.079	0.072
2–36 months	10	0.190	0.235	0.213	0.193	0.144	0.162	0.235
3–9 years	22	0.310	0.424	0.400	0.378	0.317	0.368	0.424
10–18 years	50	0.930	0.785	0.772	0.759	0.721	0.740	0.785
Adult	70	1.010						

the application of a correction factor was the following. When the liver and the kidney weights were back extrapolated into the allometric equation, it was noted that for ≤5 kg body weight, on average the liver and kidney weights were overpredicted by 15% and for a 70-kg human adult the liver and kidney weights were underpredicted by 13% and 18%, respectively.

Method VI After evaluating the results obtained from methods I–V, method VI was introduced. This approach is basically the combination of methods I–V. The clearances of drugs were predicted using a specific method for a given age. If the age of the child is ≤1 year, no exponent (or 1.0) was used on the ratio of child and adult body weight (equation 2). If the age of the child is >1 but ≤5 years, method V was used (equation 5). For chil-

Table 1c
Predicted and observed clearance (l h^{-1}) in children using different methods

Drugs/age	Body weight (kg)	Obs CL (l h^{-1})	Pred CL (0.75)	Pred CL (0.8)	Pred CL (0.85)	Pred CL (1.0)	Pred CL L + K	Pred CL (mixed)
Erythromycin estolate								
1.5 days	3	1.990	3.233	2.762	2.359	1.471	1.740	1.471
15 days	3.5	1.910	3.629	3.124	2.690	1.716	1.984	1.716
0.29 days	4	2.330	4.011	3.476	3.013	1.961	2.222	1.961
19 months	11	2.750	8.566	7.809	7.119	5.393	6.944	6.944
Adult	70	34.320						
Tiagabine								
Valproate 6 years	22.7	5.760	3.532	3.339	3.156	2.666	3.079	3.532
Adult	70	8.220						
Induced 6 years	24.5	12.420	13.269	12.590	11.947	10.206	11.655	13.269
Adult	70	29.160						
Omeprazole								
0.25–1 year	7	2.820	5.602	4.992	4.449	3.150	3.774	3.150
0.3–1.6 years	10	3.470	7.320	6.641	6.025	4.500	5.111	5.111
4–15 years	30	7.710	16.685	15.993	15.330	13.500	14.955	16.685
Adult	70	31.500						
Gabapentin								
1–59 months	11	4.780	6.215	5.665	5.165	3.913	5.038	5.038
60–155 months	36	9.420	15.122	14.627	14.149	12.806	13.804	15.122
Adult	70	24.900						
Linezolid								
Preterm <1 week	2	0.240	0.496	0.415	0.348	0.204	0.256	0.204
Full term <1 week	3	0.680	0.673	0.575	0.491	0.306	0.362	0.306
Full term >1 week <28 days	4	1.220	0.834	0.723	0.627	0.408	0.462	0.408
>28 days to <3 months	5.5	1.780	1.060	0.933	0.822	0.561	0.697	0.561
3 months to 11 years	20	4.560	2.790	2.621	2.462	2.040	2.401	2.790
12–17 years	55	6.930	5.959	5.887	5.817	5.610	5.676	5.959
Adult	70	7.140						
Lamivudine								
<2 years	10	11.600	6.878	6.240	5.662	4.229	4.802	4.802
2–6 years	15	15.900	9.323	8.632	7.992	6.343	7.796	9.323
6–12 years	30	28.800	15.679	15.028	14.405	12.686	14.053	15.679
12–18 years	50	35.500	22.998	22.615	22.237	21.143	21.697	22.998
Adult	70	29.600						
Ciprofloxacin								
3 months to 1 year	6.9	4.020	4.926	4.387	3.907	2.760	3.314	2.760
Sepsis 1–5 years	12.6	7.010	7.738	7.102	6.518	5.040	6.358	7.738
Adult	70	28.000						

dren >5 years, the allometric exponents of 0.75, 0.80 or 0.85 were used (equation 2).

Statistical analysis

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

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

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

$$\text{Mean square error (MSE)} = \Sigma(\text{predicted} - \text{observed})^2/n \quad (7)$$

$$\text{RMSE} = (\text{MSE})^{1/2} \quad (8)$$

RMSE was expressed as percent of mean using equation 9:

Table 1d
Predicted and observed clearance (l h^{-1}) in children using different methods

Drugs/age	Body weight (kg)	Obs CL (l h^{-1})	Pred CL (0.75)	Pred CL (0.8)	Pred CL (0.85)	Pred CL (1.0)	Pred CL L + K	Pred CL (mixed)
Ciprofloxacin, urinary tract								
<1 year	7.7	7.580	9.667	8.657	7.752	5.567	6.575	5.567
1year	11	12.080	12.632	11.515	10.498	7.953	10.240	10.240
2–5 years	15.9	16.500	16.652	15.462	14.358	11.496	14.006	14.006
≥6 years	22.5	32.940	21.605	20.413	19.287	16.268	18.815	21.605
Adult	70	50.610						
Cisapride								
Mean postnatal age 31 days	1.74	0.790	1.780	1.480	1.230	0.707	0.908	0.707
41 days	2.96	2.230	2.652	2.264	1.933	1.203	1.426	1.703
77 days	4.52	3.820	3.643	3.177	2.770	1.836	2.043	2.482
Adult	70	28.440						
Oxycodone								
2.3–4.7 years	15.9	14.480	15.398	14.298	13.277	10.630	13.000	13.000
6.1–9.8 years	25.2	22.870	21.751	20.667	19.638	16.848	19.230	21.751
Adult	70	46.800						
Irbesartan								
1–5 years	20.2	5.580	4.567	4.292	4.033	3.347	3.949	3.949
6–12 years	53.5	12.000	9.482	9.355	9.231	8.866	9.041	9.482
13–17 years	80.3	14.400	12.858	12.946	13.036	13.307	12.769	12.858
Adult	70	11.600						
Darbepoetin alfa								
I.v. 1–16 years	35.3	0.081	0.066	0.064	0.061	0.055	0.060	0.066
Adult	70	0.112						
S.c. 1–16 years	35.3	0.150	0.180	0.173	0.168	0.151	0.164	0.180
Adult	70	0.300						
Celecoxib								
<10 years	25.5	28.050	16.412	15.603	14.835	12.750	14.527	16.412
>10 years	49	34.300	26.785	26.312	25.846	24.500	25.314	26.785
Adult	70	35.000						
Trovafloxacin								
0.6 years	6	0.890	1.076	0.951	0.841	0.582	0.716	0.582
1.75–4 years	15	2.710	2.139	1.980	1.833	1.455	1.795	1.795
8.5–12.5 years	30	3.390	3.597	3.447	3.304	2.910	3.236	3.597
Adult	70	6.790						
Ketoprofen								
0.6–7.75 years	22	1.540	2.116	1.997	1.884	1.584	1.845	1.845
Adult	70	5.040						

$$\%\text{RMSE} = \text{RMSE} \times 100/\text{mean observed} \quad (9)$$

Results

The predicted and observed clearance values in children for 41 drugs (124 observations) are summarized in Table 1. The results of the study indicate that the use of exponent 0.75 is not suitable for the prediction of clearance for children in all age groups. Similarly, the use of exponents 0.80, 0.85 and 1.0 as well as the proposed method based on the liver and kidney weights produced variable results. All methods exhibited uncertainty in the prediction of drug clearance in children. No single method was suitable for all drugs or for all age groups. The percent errors in the prediction for all six methods are shown in Table 2. The %RMSE (Table 3) for methods I–VI was 53.86 (exponent 0.75), 53.30 (exponent 0.80), 54.72 (exponent 0.85), 65.59 (exponent 1.0), 55.31 (liver and kidney weight approach) and 48.93 (mixed approach), respectively. The %RMSE was almost similar for exponents 0.75, 0.80 and 0.85 as well as the approach based on the liver and kidney weights. The highest %RMSE in the

Table 1e
Predicted and observed clearance (l h^{-1}) in children using different methods

Drugs/age	Body weight (kg)	Obs CL (l h^{-1})	Pred CL (0.75)	Pred CL (0.8)	Pred CL (0.85)	Pred CL (1.0)	Pred CL L + K	Pred CL (mixed)
Indomethacin								
7–28 days (premature)	3	0.025	0.554	0.473	0.404	0.252	0.299	0.252
Adult	70	5.880						
Itraconazole								
0.5–2 years	11	7.940	24.110	21.979	20.037	15.180	19.618	19.618
Adult	70	96.600						
Azithromycin								
0.5–2 years	10.1	9.938	10.816	9.818	8.912	6.666	8.726	8.726
>2 <6 years	15.8	16.779	15.129	14.044	13.037	10.428	12.765	15.129
6 to <12 years	39	37.440	29.793	28.934	28.100	25.740	27.520	29.793
12 to <16 years	63.5	45.339	42.944	42.735	42.527	41.910	41.654	42.944
Adult	70	46.200						
Gentamicin								
1–7 days premature	2	0.103	0.444	0.371	0.311	0.182	0.229	0.182
7–28 days (premature)	3	0.309	0.601	0.514	0.439	0.274	0.324	0.274
1 day term	3	0.178	0.601	0.514	0.439	0.274	0.324	0.274
1–7 days (term)	3	0.248	0.601	0.514	0.439	0.274	0.324	0.274
7–28 days (term)	4	0.437	0.746	0.647	0.560	0.365	0.413	0.365
Adult	70	6.384						

prediction was seen with exponent 1.0 or with no exponent on the body weight. The lowest %RMSE was with the mixed approach, although not substantially different from other approaches (with the exception of exponent 1.0).

Further assessment of the suitability of the methods was done by grouping all 124 observations according to %error (Table 3). The number of observations were grouped as errors ≥100%, 50–99%, 31–49% and ≤30%. There were 35 observations (highest) for the exponent of 0.75 for which error in the prediction was ≥100%, whereas there were only 13 (lowest) observations ≥100% for the exponent 1.0. There were 17 observations for method V (liver and kidney weights) and 16 observations for method VI (mixed), for which error was ≥100%. The error between 50 and 99% was the least for exponent 0.75 (12 observations) and the highest for exponent 1.0 (23 observations). The number of observations for <50% error was 76, 83, 81, 87, 91 and 93 for the exponents 0.75, 0.80, 0.85, 1.0, liver and kidney weight approach and the mixed method, respectively (Table 3).

The current analysis of the data indicates that the exponent 0.75 predicts drug clearance with a fair degree of accuracy when the children are older than 5 years. As the body weight of children increased, in most cases the accuracy of the prediction using the exponent 0.75 increased. For children ≤1 year old, the exponent 0.75 overpredicted the clearance by several fold. When children were between 1 and 5 years, in most cases the prediction error remained over 50% with exponent 0.75. On the other hand, when exponent 1.0 (or no exponent) was used on the body weight, the prediction of clearance was fairly reasonable and far less erratic than 0.75 for the age group ≤1 year. For this age group, the best prediction was obtained using no exponent (or 1.0) on the body weight. With increasing age, the error in the prediction increased with exponent 1.0 on the body weight. The approach of liver and kidney weight produced far less error than the exponent of 0.75 for children in the age group of ≤1 but was more erratic than exponent 1.0. For the age group between 1 and 5, the best approach appeared to be the liver and kidney weights. Based on these observations, a mixed approach is proposed (method VI), as in this report at least it appears to be the best. There were 93 observations (75%) across all age groups with <50% error when the mixed approach was used, whereas there were 76 observations (61%) across all age groups when the exponent 0.75 was used. When compared across all methods used in this report, based on the error ≥50% or <50% (Table 3), the worst approach was the exponent 0.75. It should be noted, however, that there were 74 observations in

Table 2a
Percent error in predicted and observed clearance in children using different methods

Drugs/age	Pred CL (0.75)	Pred CL (0.80)	Pred CL (0.85)	Pred CL (1.0)	Pred CL L + K	Pred CL (mixed)
Theophylline						
1–7 days (premature)	–443	–354	–280	–123	–180	–123
7–28 days (premature)	–179	–139	–104	–27	–50	–27
1–7 days	–395	–326	–267	–133	–170	–133
7–28 days	–271	–223	–182	–87	–107	–87
1–3 months	–122	–95	–71	–15	–26	–15
2–5 years	19	25	30	45	32	32
6.5–12 years	17	22	26	37	28	17
Antipyrine						
<12 years	14	20	25	39	27	14
>12 years	1	5	9	20	12	1
Lorazepam						
<1 year	–860	–719	–600	–336	–417	–336
2–12 years	–13	–5	2	20	4	4
>12–18 years	–23	–17	–13	1	–10	–23
Famotidine						
0–3 months	–335	–277	–227	–113	–141	–113
>3–12 months	–67	–48	–32	8	–12	8
1.1–12.9 years	–39	–30	–22	–1	–19	–19
Levofloxacin						
I.v. 0.5 to <2 years	29	36	42	57	51	51
2 to <5 years	30	35	40	53	42	42
5 to <10 years	22	26	30	40	32	22
10 to <12 years	12	14	16	21	18	12
12–16 years	12	13	14	17	16	12
Lamotrigine						
<6 years	2	9	16	33	18	2
>6 years (3.8–11.3 years)	–18	–14	–11	0	–8	–18
Amprenavir						
4–12 years	26	29	33	42	34	26
Gatifloxacin						
0.5–2 years	3	12	21	41	33	33
2–6 years	29	34	39	50	40	29
6–12 years	25	28	31	39	32	25
12–16 years	13	15	16	21	18	13

children ≤5 years. This may be the reason that the use of exponent 0.75 appears to be the worst. The exponents of 0.80 and 0.85 produced similar results to those seen with exponent 0.75 across all age groups (slightly better at the lower age group and slightly more erratic at the higher age group).

A thorough scrutiny of Table 1 indicates that the clearance in children increases with age and body weight. Normalization of clearance based on per kg body weight may indicate that children have higher or equal clearance than adults. This is a misconception, as was rightly pointed out by Holford [3] several years ago. Therefore, dosing in children should be based on total body clearance rather than clearance per kg body weight.

Discussion

The pharmacokinetics and pharmacodynamics of a drug may differ between adults and children. These differences are mainly due to the physiological and biochemical differences between infants, children, adolescents and adults. The ontogenesis of the clearance mechanism may be the most critical determinant of a pharmacological response in infants and children [12, 13]. Numerous articles have outlined the developmental changes in children and the need to predict drug

Table 2b
Percent error in predicted and observed clearance in children using different methods

Drugs/age	Pred CL (0.75)	Pred CL (0.80)	Pred CL (0.85)	Pred CL (1.0)	Pred CL L + K	Pred CL (mixed)
Caffeine						
1–7 days (premature)	–3046	–2531	–2100	–1192	–1523	–1192
7–28 days (premature)	–1439	–1214	–1022	–600	–728	–600
1–3 months	–225	–185	–150	–68	–84	–68
3–12 months	–41	–26	–13	18	4	18
Vancomycin						
7–28 days (premature)	–164	–125	–92	–20	–42	–20
1–7 days (term)	–251	–200	–156	–60	–89	–60
7–28 days (term)	–184	–146	–113	–39	–57	–39
1–3 months	–29	–13	1	34	27	34
3–12 months	–37	–23	–11	20	6	20
Cefetamet						
I.v. 3–5 years	9	16	22	37	24	24
5.5–12 years	3	7	10	21	12	3
Chloramphenicol						
Premature	–400	–318	–250	–105	–158	–105
Infant	–174	–141	–111	–42	–56	–56
Child	–211	–192	–174	–127	–167	–167
Valproic acid						
0–2 months	–94	–69	–49	0	–10	0
2–36 months	–24	–12	–2	24	15	–24
3–9 years	–37	–29	–22	–2	–19	–37
10–18 years	16	17	18	22	20	16
Erythromycin estolate						
1.5 days	–62	–39	–19	26	13	26
15 days	–90	–64	–41	10	–4	10
0.29 days	–72	–49	–29	16	5	16
19 months	–211	–184	–159	–96	–153	–153
Tiagabine						
Valproate 6 years	39	42	45	54	47	39
Induced 6 years	–7	–1	4	18	6	–7
Omeprazole						
0.25–1 year	–99	–77	–58	–12	–34	–12
0.3–1.6 years	–111	–91	–74	–30	–47	–47
4–15 years	–116	–107	–99	–75	–94	–116

clearance in children in order to select an optimal dose [13, 14]. Several methods [12, 15, 16], have been suggested to predict the clearance in children from adult data and one of these methods is based on the allometric size model [2]. This model uses a fixed exponent of 0.75 based on Kleiber's original work relating basal metabolic rate against body weight across several species. However, a systematic evaluation of exponent 0.75, to determine if indeed this is the most suitable exponent to predict drug clearance in children from adults, has not been performed. The current study evaluates not only the predictive performance of a fixed exponent of 0.75 but also other exponents such as 0.85 and 0.80, as well as no exponent on the body weight. All three exponents (0.75, 0.80 and 0.85) produced some 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 clearance in children is inaccurate. There were some drugs that were predicted with greater accuracy by 0.75 than by 0.80 or 0.85, and *vice versa*. It is difficult to determine *a priori* which exponent is suitable for a given drug. One should recognize that the exponents of allometry have no physiological meaning [8]. The exponents of clearance for a given drug are not universal and will vary depending on the species and

Table 2c
Percent error in predicted and observed clearance in children using different methods

Drugs/age	Pred CL (0.75)	Pred CL (0.80)	Pred CL (0.85)	Pred CL (1.0)	Pred CL L + K	Pred CL (mixed)
Gabapentin						
1–59 months	–30	–19	–8	18	–5	–5
60–155 months	–61	–55	–50	–36	–47	–61
Linezolid						
Preterm <1 week	–107	–73	–45	15	–7	15
Full term <1 week	1	15	28	55	47	55
Full term >1 week <28 days	32	41	49	67	62	67
>28d- <3 month	40	48	54	68	61	68
3 month-11 years	39	43	46	55	47	39
12–17 years	14	15	16	19	18	14
Lamivudine						
<2 years	41	46	51	64	59	59
2–6 years	41	46	50	60	51	41
6–12 years	46	48	50	56	51	46
12–18 years	35	36	37	40	39	35
Ciprofloxacin						
3 months to 1 year	–23	–9	3	31	18	31
Sepsis 1–5 years	–10	–1	7	28	9	–10
Urinary tract						
<1 year	–28	–14	–2	27	13	27
1 year	–5	5	13	34	15	15
2–5 years	–1	6	13	30	15	15
≥6 years	34	38	41	51	43	34
Cisapride						
Mean postnatal age 31 days	–125	–87	–56	11	–15	11
41 days	–19	–2	13	46	36	24
77 days	5	17	27	52	47	35
Oxycodone						
2.3–4.7 years	–6	1	8	27	10	10
6.1–9.8 years	5	10	14	26	16	5
Irbesartan						
1–5 years	18	23	28	40	29	29
6–12 years	21	22	23	26	25	21
13–17 years	11	10	9	8	11	11

sample size used in the allometric scaling [8, 10]. Due to the very nature of the exponents of allometry, it is not surprising that one single exponent does not predict drug clearance in children across all ages. Had Kleiber used more species in his work, he might have found a very different exponent for basal metabolic rate than 0.734. Therefore, the notion that 0.75 will give the best result for the prediction of clearance from adults to children (and also from one species to another, e.g. from one laboratory animal to humans) is inaccurate. One can clearly observe in this study that the exponents 0.80 and 0.85 provide almost the same degree of accuracy or error in the prediction of clearance in children as the exponent 0.75.

The study also indicates that a single exponent may not be suitable for the prediction of drug clearance in children of all ages from adult data; therefore, a combination of methods is recommended in order to improve the prediction. It appears that for children ≤1 year old, a better approach is to use no exponent on the ratio of children and adult body weight. The three exponents (0.75, 0.80 and 0.85) systematically overpredicted the clearances of most drugs in children aged ≤1 year, but as the exponent increased from 0.75 towards 1.0, the error in prediction decreased. Similarly, the liver + kidney approach (method V) appeared to predict clearance better than any of the three exponents for the age group between >1 and 5 years. After age 5, one can use any

Table 2d
Percent error in predicted and observed clearance in children using different methods

Drugs/age	Pred CL (0.75)	Pred CL (0.80)	Pred CL (0.85)	Pred CL (1.0)	Pred CL L + K	Pred CL (mixed)
Darbepoetin alfa						
I.v. 1–16 years	19	21	25	32	26	19
S.c. 1–16 years	–20	–15	–12	–1	–9	–20
Celecoxib						
<10 years	41	44	47	55	48	41
>10 years	22	23	25	29	26	22
Trovafloxacin						
0.6 years	–21	–7	6	35	20	35
1.75–4 years	21	27	32	46	34	34
8.5–12.5 years	–6	–2	3	14	5	–6
Ketoprofen						
0.6–7.75 years	–37	–30	–22	–3	–20	–20
Indomethacin						
7–28 days (premature)	–2116	–1792	–1516	–908	–1096	–908
Itraconazole						
0.5–2 years	–204	–177	–152	–91	–147	–147
Azithromycin						
0.5–2 years	–9	1	10	33	12	12
>2 to <6 years	10	16	22	38	24	10
6 to <12 years	20	23	25	31	26	20
12 to <16 years	5	6	6	8	8	5
Gentamicin						
1–7 days premature	–331	–260	–202	–77	–122	–77
7–28 days (premature)	–94	–66	–42	11	–5	11
1 day term	–238	–189	–147	–54	–82	–54
1–7 days (term)	–142	–107	–77	–10	–31	–10
7–28 days (term)	–71	–48	–28	16	5	16

Table 3
Percent root mean square error (RMSE) and percent error in the prediction of clearance in children by several methods

Error %RMSE % error	Exp 0.75 53.86	Exp 0.80 53.30	Exp 0.85 54.72	Exp 1.0 65.59	L + K wt 55.31	Mixed 48.93
≥100	35	29	25	13	17	16
50–99	12	14	16	23	16	15
31–49	16	17	20	30	24	21
≤30	61	64	63	57	67	72
≥50	47	43	41	36	33	31
<50	76	81	83	87	91	93

of the three exponents (0.75, 0.80 and 85) to achieve a reasonably good prediction of clearance in children. Therefore, a combination of approaches is suggested which may help in improving the prediction of clearance in children from adult data:

- If the age of a child is ≤1 year old, no exponent should be used in equation 2.
- If the age of a child is >1 but ≤5 years old, method V should be used.
- For children >5 years old, exponents 0.75, 0.80 or 0.85 can be used.

It should be noted, however, that all the aforementioned methods, under the conditions described above, may help in reducing the prediction error but not neces-

sarily provide an accurate prediction of drug clearance in children. For example, the prediction error in morphine clearance in children <1 week was 377% when predicted using exponent 0.75 but 126% without the use of any exponent. Certainly, there was a substantial improvement in the prediction but the error in the prediction was still substantial. It should also be emphasized that the above rules are also not perfect. For example, for children in the age group 2–6 months, morphine clearance was best predicted with the exponent of 0.85 (error 1%), but due to the above-mentioned rule, exponent 1.0 was considered the best method (error 31%). This kind of uncertainty was observed with many drugs but for the majority of drugs the rules appeared to work fairly well. The main objective here is to find a method or combination of methods that can reduce the prediction error. One important question remains unresolved: what an acceptable prediction error is in drug clearance for children? Since weight- or body surface area-based dosing in children may not be suitable, it is important that the clearance of a drug in children be predicted as accurately as possible. Probably, <50% error in the predicted clearance will be acceptable but this must be verified by further work.

References

1 Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology—drug disposition, action, and therapy in infants and children. N Engl J Med 2003; 349: 1157–67.

2 Anderson BJ, McKee AD, Holford NH. Size, myths and the clinical pharmacokinetics of analgesia in paediatric patients. Clin Pharmacokinet 1997; 33: 313–27.

3 Holford NH. A size standard for pharmacokinetics. Clin Pharmacokinet 1996; 30: 329–32.

4 Kleiber M. Body size and metabolism. Hilgardia 1932; 6: 315.

5 Mahmood I. On the exponents of Allometry. In: Interspecies Pharmacokinetic Scaling. Principles and Application of Allometric Scaling, Rockville, MD: Pine House Publishers 2005: 86–90.

6 Taylor CR, Maloiy GM, Weibel ER, Langman VA, Kamau JM, Seeherman HJ, Heglund NC. Design of the mammalian respiratory system III. Scaling maximum aerobic capacity to body mass: wild and domestic mammals. Resp Physiol 1981; 44: 25–37.

7 Nawaratne S, Brien JE, Seeman E, Fabiny R, Zalcberg J, Cosolo W, Angus P, Morgan DJ. Relationships among liver and kidney volumes, lean body mass and drug clearance. Br J Clin Pharmacol 1998; 46: 447–52.

8 Mahmood I. Interspecies scaling of clearance. In: Interspecies Pharmacokinetic Scaling. Principles and Application of Allometric Scaling, Rockville, MD: Pine House Publishers 2005: 39–85.

9 White CR, Seymour RS. Allometric scaling of mammalian metabolism. J Exp Biol 2005; 208: 1611–9.

10 White CR, Seymour RS. Sample size and mass range effects on the allometric exponent of basal metabolic rate. Comp Biochem Physiol A Mol Integr Physiol 2005; 14: 74–8.

11 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.

12 Alcorn J, McNamara PJ. Ontogeny of hepatic and renal systemic clearance pathways in infants: part I. Clin Pharmacokinet 2002; 41: 959–98.

13 Alcorn J, McNamara PJ. Ontogeny of hepatic and renal systemic clearance pathways in infants: part II. Clin Pharmacokinet 2002; 41: 1077–94.

14 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.

15 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.

16 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.