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Maturation and Growth of Renal Function: Dosing Renally Cleared Drugs in Children

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ABSTRACT A model was developed that characterized the maturation and growth of the renal function parameters (RFPs) glomerular filtration rate (GF), active tubular secretion (AS), and renal plasma flow (Q_R). Published RFP values were obtained from 63 healthy children between the ages of 2 days and 12 years. Maturation over time was assumed to be exponential from an immature (RFP_{im}) to a mature (RFP_{ma}) level; for growth, RFP_{im} and RFP_{ma} were assumed to follow the allometric equation:

$$RFP(age, W) = aW^b e^{-kmat*age} + cW^b (1 - e^{-kmat*age}),$$

where W is body weight, k_{mat} is the maturation rate constant, b is the body weight exponent, and a and c are RFP_{im} and RFP_{ma} at unit W. The model-based equation was fitted to the age-W, RFP values by a nonlinear least-squares method. For GF, the maturation half-life was 7.9 months (90% maturation, 26 months), the body weight exponent was 0.662, and the ratio c/a (which reflected the magnitude of the maturation influence) was 3.1. For AS and Q_R, the maturation half-lives were about 3.8 months and the ratio c/a was about 1.8. For renally eliminated drugs, the model can be used to estimate dosing regimens that are based on the adult dosing regimen and the age and weight of the child.

KEYWORDS: Renal Function.

INTRODUCTION Dosing regimens are usually devised to maintain the drug plasma concentration within the therapeutic window[1] . The dosing regimen is commonly based on the product of the total body clearance and the desired plasma concentration. Although the total body clearances of most drugs are available for adults[2] , there is little quantitative information about clearance values in infants and children[3] . Consequently, when drug clearance values are unknown in the pediatric patient, the suggested dosing rate is the product of the adult dosing rate (DR) and the fraction of the adult body surface area (BSA) of the child; ie, $DR_{child} = 1.4\ DR_{adult}\ (BSA_{child}\ [m^2]/1.8\ m^2)$[4] . Implicit in this calculation is the assumption that the total body clearance of the drug is directly proportional to the body surface area in adults and children; ie, proportional to body weight to the two-thirds power.

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For renally eliminated drugs, clearance values in children follow the body surface area relationship reasonably well, although caution is recommended for very young children because clearance mechanisms are thought to be immature at birth, and the immaturity is thought to persist for several months until the adult clearance capacity is achieved[5] . For example, the influence of immaturity was apparent in the total body clearance values for the renally eliminated antibiotic cefetamet [6] . The expected linear relationship between clearance and body weight on log-log coordinates was observed for children above the age of 4 years, but the clearance values in younger children deviated negatively from the line.

Although both maturation and growth are involved in the age-associated increase in renal clearance capacity, there has been no analysis that shows quantitatively the individual influences of the 2 processes. In this report, a model that separately accounted for maturation and growth influences was applied to renal function parameters from the literature.

MATERIALS AND METHODS

Renal Function Parameters

Values for glomerular filtration rate (GF), active tubular secretion (AS), and renal plasma flow (Q_R) were from Rubin et al, in which cross-sectional data were reported from 63 normal well children between the ages of 2 days and 12 years[7] . GF was the mannitol clearance, which was determined by intravenous injection of mannitol and removal of at least 3, and usually 4, serial blood samples beginning at 20 minutes postinjection. When plotted versus time on semilogarithmic coordinates, the plasma concentrations of mannitol fell along a straight line. The plasma concentration at the midpoint of serial urine collections minus 2 minutes was interpolated from the plot and used along with the amount of mannitol in the urine sample to calculate the clearance, from the relationship GF = excretion rate of mannitol divided by its plasma concentration. At least 2 and generally 3 or 4 successive estimations of GF were made and averaged to make the final GF value for each subject.

Q_R was determined simultaneously with GF, by administration of a low dose of p-aminohippuric acid (PAH) with the mannitol and determination of its renal clearance, which was taken as a measure of Q_R. AS was determined as the renal clearance of PAH after a high dose. The maximum rate of PAH renal elimination was determined and the elimination of PAH by glomerular filtration was subtracted to give AS. Both Q_R and AS were the averages of at least 2 and generally 3 or 4 serial determinations.

Model of Maturation and Growth

To discriminate among maturation and growth, a model that separated the 2 influences was used[6] . Each renal function parameter (RFP) was assumed to have at birth an immature value (RFP_{im}) that increased exponentially with age to the mature value (RFP_{ma}) (**Figure 1**). The maturation part of the model assumed the following RFP-age relationship:

$RFP(age) = RFP_{im}\ e^{-kmat*age} + RFP_{ma}\ (1 - e^{-kmat*age})$. [Equation 1]

The first-order rate constant k_{mat} determined the rate at which RFP_{im} approached RFP_{ma}. To incorporate the influence of body weight, both RFP_{im} and RFP_{ma} were assumed to follow the allometric equation[8] . The body weight exponent (b) value in Equations 2 and 3, which related RFP_{im} and RFP_{ma} to body weight (W), was assumed to be the same for both:

$RFP_{im} = a\ W^b$ [Equation 2]

$RFP_{ma} = c\ W^b$ [Equation 3]

where a and c are the values of RFP_{im} and RFP_{ma} at unit body weight.

Equations 2 and 3 were used in Equation 1 to give Equation 4, which allowed RFP to increase as a result of both maturation and growth:

$RFP\ (age, W) = a\ W^b\ e^{-kmat*age} + c\ W^b\ (1 - e^{-kmat*age})$. [Equation 4]

Estimation of Model Parameters

Values of the RFPs appeared to increase with age as a consequence of maturation of renal function, as well as increased body size (see Results). Equation 4 was fitted by nonlinear least squares to RFP values determined in 63 subjects that ranged in age from 2 days to 142 months and in body weight from 2.15 to 35.5 kg. The WinNonlin computer program, ver. 1.1 (Scientific Consulting, Lexington, KY), was used. Both age and body weight were independent variables; the parameters were a, b, c, and k_{mat}, and the weighting function was Y^{-2}.

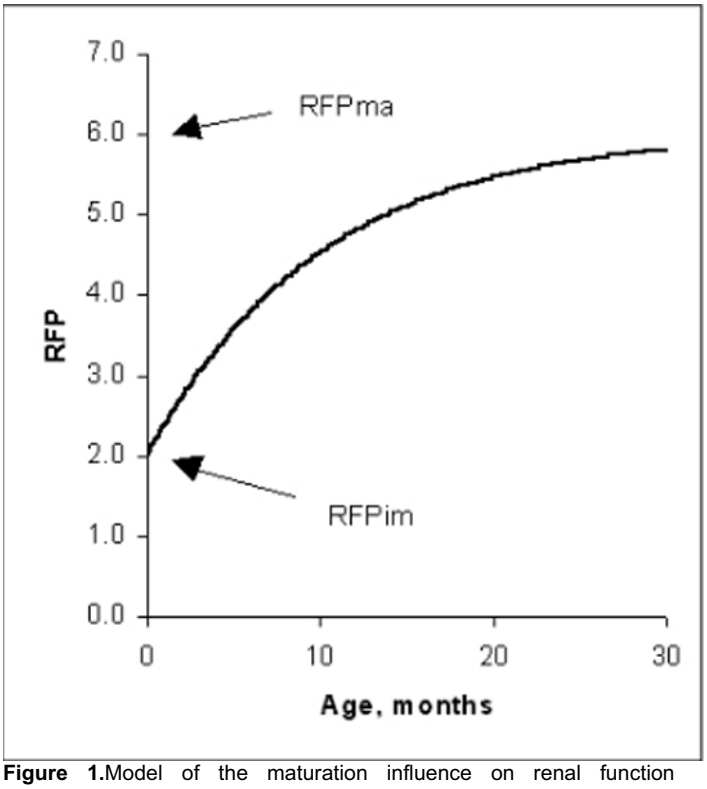

Figure 1. Model of the maturation influence on renal function parameters. RFP was simulated using Equation 1; RFP_{im} and RFP_{ma} values were 2 and 6, and the value of k_{mat} was 0.1 $months^{-1}$.

RESULTS

When the RFPs were plotted versus body weight on log-log coordinates, the relationships appeared linear for the older children. For example, **Figure 2** shows GF values and the linear regression line (solid line) for age above 2 years. Values from children below the age of 2 years generally fell below the extrapolated line based on the GF values from the older children, and this negative deviation was attributed to immaturity of GF function. Use of Equation 4 to model the influence of both maturation and growth accounted for immaturity; the fit of Equation 4 to the data shown in **Figure 2** is characterized in **Figure 3**, which shows the model-predicted GF values plotted versus the observed values. (Because Equation 4 has 2 independent variables [age and weight], the fit of the equation could not be shown in **Figure 2**.)

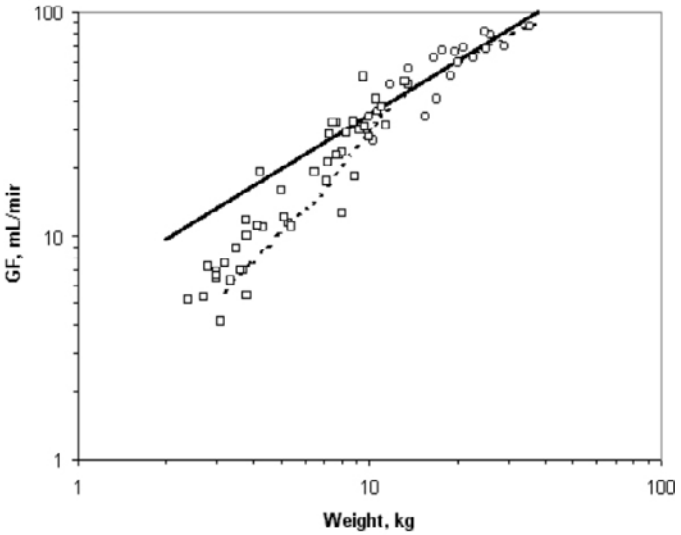

Figure 2. Glomerular filtration rate plotted versus body weight. The solid line represents the regression of log GF versus log W for age above 2 years. Open circle, age>2 years; open square, age <2 years; the dashed line shows values predicted using Equation 4 with the parameter values from Table 1 and average weight for age values from Table 2. The fit of Equation 4 to the observed GF values was not displayed here because the equation used 2 independent variables (age and weight), and both of them could not be displayed.

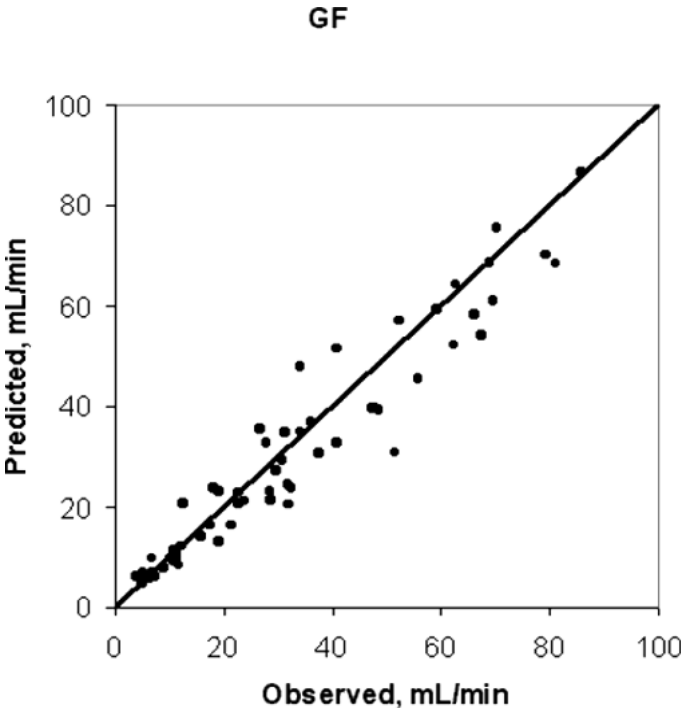

Figure 3.GF values predicted by Equation 4 versus the observed GF values, along with the line of identity.

The points appeared to scatter randomly about the line of identity for the entire data set, although several of the points appeared to be displaced significantly from the line. Of the 63 points shown, 33 lay within ±15% of the line, 18 lay between ±15% to ±25%, and 12 were displaced more than ±25% from the corresponding line value. The displacement of the points from the line reflects unaccounted for factors in addition to maturation

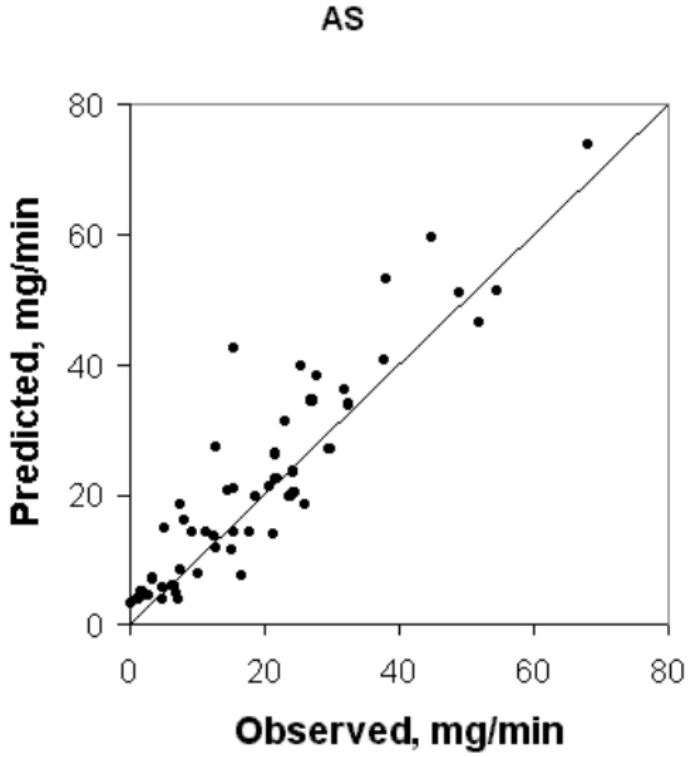

Figure 4.AS values predicted by Equation 4 versus the observed AS values, along with the line of identity.

and growth, such as interindividual variability in the 4 model parameters and experimental errors. Similar plots for AS and Q_R are shown in **Figures 4** and **5**, and the model parameter values from the fits are shown in **Table 1**. Also shown in **Figure 2** (dashed line) are the GF values predicted for average weight for age subjects.

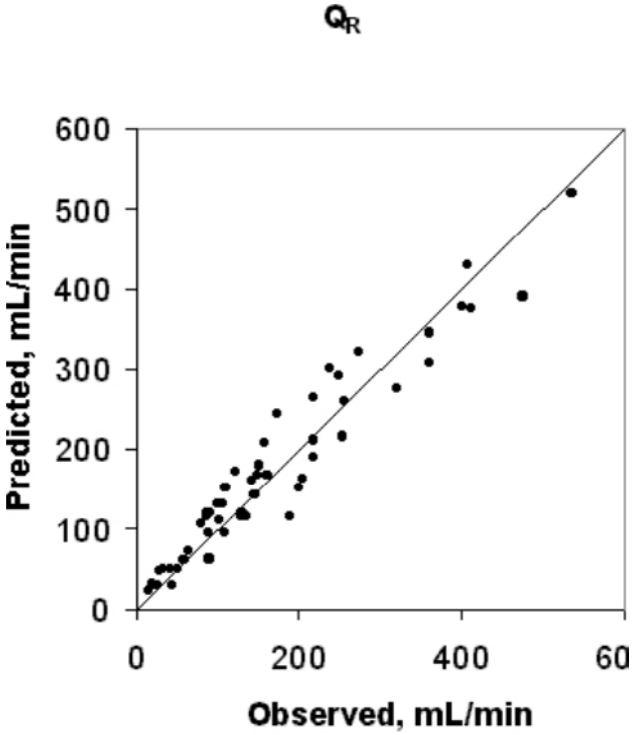

Figure 5.Q_R values predicted by Equation 4 versus the observed Q_R values, along with the line of identity.

Table 1. Model parameter values ±CV%* from the least-squares fit of the maturation-growth model (Equation 4) to glomerular filtration rate (GF), active tubular secretion activity (AS), and renal blood flow (QR)

RFP	a	c	c/a	b	k_{mat} [mo^{-1}]	$t_{1/2,mat}$ [mo]	Corr
GF [mL/min]	2.60 ±16%	8.14 ±40%	3.13	0.662 ±20%	0.0822 ±32%	7.86	0.964
AS [mg/min]	1.08 ±34%	1.83 ±64%	1.69	1.04 ±22%	0.185 ±132%	3.75	0.917
Q_R [mL/min]	10.2 ±19%	19.8 ±35%	1.94	0.916 ±13%	0.178 ±58%	3.89	0.964

*Coefficient of variation, calculated as the standard deviation of the parameter divided by the parameter value, expressed as a percentage.

DISCUSSION

The discovery of a method to normalize renal function over the preadult period has important practical implications for the development of dosing regimens for renally cleared drugs. Rubin et al examined the RFPs used here in regard to body weight, body height, body surface area, average kidney weight, and average basal metabolic rate. None of these factors individually accounted for the changes observed in infants and children[7] . Hallynck et al examined a compilation of creatinine clearances from 5,146 normal subjects (from 68 publications) ranging in age over the entire life span[9] . Normalization to body weight, lean body mass, and body surface area did not produce a unifying value for this parameter. More recently, linear regression techniques were used to develop an empirical mathematical model that related GF to age and weight[10] . Although this model predicted GF using the age and weight of the subject, it failed to "disentangle" age and weight[11] and did not provide insight into the kinetics of maturation as separate from the kinetics of growth.

The model presented here separates and quantifies the influence of maturation from the influence of growth on the RFPs. The *degree* of maturation of the RFPs is indicated by the ratio c:a, which was 3.1 for GF, as contrasted with 1.7 and 1.9 for AS and Q_R (**Table 1**). In the absence of growth, the renal clearance capacities of filtration and active secretion (intrinsic transport capacity and flow-limited capacity) would increase by these factors, with increasing age attributable solely to maturation. In other words, the GF capacity per unit body weight at birth was 32% of the mature capacity. The time for maturation, as characterized by the maturation half-life, can be taken as 3.3 $t_{1/2,mat}$ (time for 90% maturation), or about 2 years for GF and 1 year for AS and Q_R.

The body weight exponent, b, for growth of GF was near the value of two thirds, which suggested that GF growth paralleled the body surface area. In contrast, b-values for AS and Q_R were near 1, and growth of active secretion, therefore, appeared to parallel body weight.

To examine the influences of maturation and growth on the RFPs, average body weights for age were taken from the literature[12] (**Table 2**). Values for male and female subjects were similar and averaged. These age and weight values were used with the parameters shown in **Table 1** to calculate with Equation 4 the value of each RFP as a function of age (**Table 2**) and for GF (**Figure 2**). When these values were expressed per kg body weight and divided by the corresponding model-predicted young-adult values (W = 70 kg, age = 240 months), the profiles in **Figure 6** were obtained. The fractional GF was near 1 at birth; ie, GF per kg body weight was near the young-adult value at birth. Subsequently, GF was influenced positively by maturation and negatively by growth, over 2 time frames. Maturation had the greater influence initially, with the GF per kg exceeding the young-adult value by nearly 70% at 30 months. The influence of maturation ended at this age while growth contined to exert its negative influence, which resulted in the decline of GF per kg to the young-adult value. Both maturation and growth acted oppositely and simultaneously during the first 2 years of life, and their net influence is apparent in **Figure 6**.

Table 2. Model-predicted values for glomerular filtration rate (GF), active secretion activity (AS), and renal plasma flow (QR) in average-weight-for-age neonates, infants, and children

	Average for age	--------GF--------		--------AS--------		--------Q_R--------	
Age in months	W, kg	mL/min	mL/min/kg	mg/min	mg/min/kg	mL/min	mL/min/kg
0.049	3.17	5.62	1.78	3.60	1.14	29.6	9.35
1	3.95	7.61	1.93	5.03	1.27	41.5	10.5
2	4.86	9.95	2.05	6.77	1.39	55.7	11.5
3	5.76	12.4	2.15	8.60	1.49	70.5	12.2
3.5	6.42	13.9	2.17	9.88	1.54	80.5	12.5
5	7.18	16.9	2.35	11.8	1.65	96.5	13.4
7	8.12	20.6	2.54	14.2	1.75	116	14.3
10	9.07	25.2	2.78	16.8	1.85	137	15.1
15	10.5	31.7	3.01	20.4	1.94	165	15.7
20	11.5	36.3	3.15	22.8	1.98	183	15.9
30	13.3	43.0	3.23	26.6	2.00	211	15.9
42	15.5	49.2	3.17	31.3	2.02	243	15.7
48	16.5	51.6	3.13	33.4	2.02	258	15.6
60	18.6	56.2	3.02	37.8	2.03	288	15.5
72	20.8	60.7	2.92	42.4	2.04	319	15.3
84	23.4	65.6	2.81	47.8	2.05	354	15.2
96	26.0	70.5	2.71	53.5	2.06	391	15.0
120	31.0	79.2	2.55	64.2	2.07	460	14.8
144	39.3	92.6	2.36	81.9	2.09	570	14.5
180	53.2	113	2.13	112	2.11	753	14.2
204	58.7	121	2.06	124	2.12	824	14.1
240	70.0	136	1.94	149	2.13	969	13.8

Table 3. Usual adult (55 years, 70 kg) dosing rate adjustment factor for renally eliminated drugs that have a high therapeutic index

Age	$FRAC_{GF}$	$FRAC_{AS}$	$FRAC_{QR}$
0-6 months	1.5	0.85	1.15
6-12 months	1.85	1.10	1.4
1-8 years	2.1	1.25	1.5
8-15 years	1.7	1.25	1.5

FRAC indicates fraction; GF, glomerular filtration rate; AS, active secretion activity; Q_R renal plasma flow.

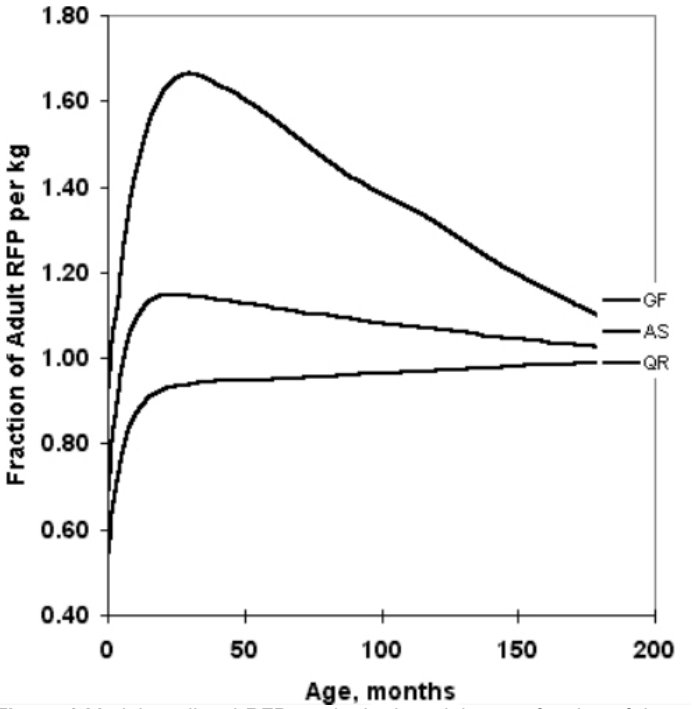

Figure 6. Model-predicted RFP per kg body weight as a fraction of the model-predicted young-adult value for average-weight-for-age children.

The profiles for AS and Q_R differ from that of GF (**Figure 6**). These RFPs per kg body weight were about half the young-adult values at birth, and they more rapidly assumed their young-adult values: AS by 12 months and Q_R by 3.5 months.

Recent concern has been expressed about the small fraction of drugs approved for use in children, even though many drugs lacking approval for children are widely used[13] . A 1999 FDA rule requires pediatric studies to generally support use of drugs in children[14] . For drugs that lack specific dosage guidelines for infants and children, the results of the analysis in this paper may be used to adapt the adult dosing regimen when the drug is renally eliminated. Multiple dosing regimens are usually based on the total body clearance such that the dosing rate is taken as the product of the clearance and the desired steady-state plasma concentration of the drug. For renally eliminated drugs, it is well accepted that the renal clearance is proportional to GF[15] . In adults with impaired renal function, surrogate measures of GF (CL_{CR}, S_{CR}) are often used to adjust the dosing rate. Extension of these concepts to adaptation of the adult regimen for the child leads to the proposition that the RFP values per kg in **Table 2**, expressed as a fraction of the adult values, could be applied to the adult mg/kg regimen to estimate the appropriate mg/kg regimen for the child. For example, for a drug that was eliminated by glomerular filtration only, a 7-month-old child of average weight for age (8.12 kg) would have a model-predicted GF of 2.54 mL/minute/kg. Using the mature-adult GF of 100 mL/minute/70 kg or 1.43 mL/minute/kg indicates that the child should have a mg/kg dosing rate that is (2.54/1.43) or 1.78 times the mature-adult mg/kg dosing rate. If the weight of the child deviated from the average, a proportional adjustment should be made; eg, if W = 10 kg, then the adjustment should be 1.78 x (10/8.12) or 2.19 times the adult mg/kg dosing rate.

The above calculation used 100 mL/minute for the normal mature-adult GF. The GF predicted using Equation 4 for a young adult (70 kg, 20 yr) was 136 mL/minute or 1.94 mL/minute/kg, which was substantially above the value of 1.43 mL/minute/kg, although in line with population average GF values in young adults of 120 to 130 mL/minute. It has been suggested that the appropriate denominator for this calculation is the GF for the typical adult patient for whom the drug would most likely be prescribed; ie, 55 years of age and 70 kg. A GF value of 85 mL/minute/70 kg has been recommended[15] , but in view of the slightly elevated young-adult GF value predicted using Equation 4, the mature-adult GF value of 100 mL/minute/70 kg seemed appropriate.

This approach can be implemented by insertion of the parameter values for GF from **Table 1** into Equation 4, dividing through the equation by W and then division by 1.43 mL/minute/kg, followed by simplification to give $FRAC_{GF}$, the fraction of the usual adult mg/kg dosing rate for a child:

$$FRAC_{GF} = W^{-0.338} (5.69 - 3.87\, e^{-0.0822*age}).$$ [Equation 5]

Insertion of the child's weight in kg and age in months into Equation 5 gives the fraction of the adult mg/kg dosage appropriate for the child. This equation explicitly includes body weight and compensates for any deviation of the child's weight from the average weight for age. Other appropriate factors such as metabolism and renal elimination of metabolites should also be considered in implementation of this approach.

CONCLUSION

For drugs eliminated by active tubular secretion, a similar approach could be taken, although it is less clear what should be the mature-adult values for AS and Q_R. In the development of Equation 5, the mature-adult value for GF was about 75% of the model-predicted young-adult value. Using 75% of the model-predicted young-adult values for AS and Q_R, the following equations give the fractions of the usual adult mg/kg dosing rate:

$FRAC_{AS} = W^{0.040} (1.14 - 0.465\ e^{-0.185*age})$ and [Equation 6]

$FRAC_{QR} = W^{-0.084} (1.90 - 0.92\ e^{-0.178*age})$. [Equation 7]

$FRAC_{AS}$ should be used in cases where the desired plasma concentration is well above the K_M of the transporter, whereas $FRAC_{QR}$ should be used when the concentration is well below the K_M. When both filtration and active tubular secretion contribute to the drug clearance, an appropriately weighted average of the $FRAC_{GF}$ and $FRAC_{AS}$ or $FRAC_{QR}$ fractions should be used. When a high therapeutic index provides a margin of safety, the adjustment factors in **Table 3** should suffice.

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