Simplified Methods for Renal Clearance in Children: Scaling for Patient Size

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Development and validation of simplified renal clearance methods has required a research data base of multiple blood samples drawn over a substantial time interval, which is difficult to obtain for children. While the medical risks entailed in drawing multiple samples may be negligible, the problems of parental and institutional consent make such studies more difficult in the pediatric population. Scaling for patient size permits combining data from patients of different age and limits the number of studies required. A scaling technique is presented and evaluated here. With scaling, adult data can be used successfully to predict pediatric responses and to develop pediatric methods based on adult data alone. Inclusion of pediatric data improves the fit and permits development of generic methods that work with both adults and children.

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Simplified renal clearance methods requiring only one or two plasma samples have proven useful for measuring renal function in adults, but have been less well studied in children. Each of these methods has been derived from a research database of blood clearance curves: multiple blood samples obtained over a substantial time interval, 3 hr or more in the case of glomerular filtration rate (GFR) agents. Such data are difficult to obtain for children because of the practical problems related to informed consent.

If the data are scaled for patient size, then measurements from patients of different size can be combined so that fewer data are required. A method of scaling is presented here. To validate it, scaled methods for orthoiodohippurate (OIH) clearance were first developed using plasma clearance curves from adults and then cross-tested against pediatric data from the literature. After thus validating the scaling procedure, adult and pediatric data were combined to create general methods valid for all patients in the study population (which included both adults and children).

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METHODS OF PROCEDURE

Iodine-131-OIH plasma clearance curves were measured in 68 adults and in 30 children of 38 lb or more. The children ranged in age from 4 to 18 yr and in weight from 38 to 227 lb (median 73 lb). Data were pooled from four prior publications, where the technical procedures were described in detail (*1–4*). We have analyzed the adult data elsewhere (*5*). One previously reported adult patient was eliminated from the present study because the weight of the patient was not recorded. Sampling ranged from six samples over 10–60 min to nine samples over 10–90 min.

A two-exponential curve was fitted to each data set and the fitted curves were used for subsequent analysis. OIH clearance was calculated from the fitted curves by the conventional Sapirstein method (*6*) except for four anephric adult patients, where the clearance was set to the true value of zero despite a small positive clearance by the Sapirstein calculation.

Clearance was calculated by two methods: (1) an empirical single-sample formula and (2) a two-sample method based on a two-compartment model. These are described in detail in the appendix. The empirical scaled formula was derived by fitting the dimensionless quantity Ft/V_E (where F represents clearance, t sample time, and V_E extracellular fluid volume) with a polynomial in the dimensionless quantity V_t/V_E (where V_t is the apparent volume of distribution at time of sampling). Since volumes are scaled by weight, weight can be substituted for volume by incorporating the constant of proportionality into the coefficients of the polynomial. One term of this polynomial corresponded to a one-compartment model. If the other terms are regarded as a correction, then this can be called a corrected one-compartment model, with the correction accounting for the effects of additional compartments.

To describe the two-compartment model, we shall follow the notation of Tauxe (*7*), with injection into compartment 1 having volume V_1, which exchanges tracer with compartment 2 at flow rate F_{12}. This model is defined by four parameters, which can be chosen in various ways that are mathematically equivalent. We have chosen as parameters the volume V_1 of compartment 1, the flow F_{13} from compartment 1 to the outside (i.e., to the bladder), and the two quantities $k_1 = F_{12}/V_1$ and $k_2 = F_{12}/V_2$. (V_2, the volume of the second compartment, is not independent and can be calculated from V_1, k_1, and k_2.)

Conventional physiologic scaling for size and species entails scaling volumes (such as extracellular fluid) by weight and scaling fluxes [such as GFR or effective renal plasma flow (ERPF) by surface area. It follows from dimensional analysis (*8*) that the sampling time should also be scaled. If volume is measured in ml and flux in ml/min, then time, which is proportional to volume/

flux, should be scaled as weight/area. Scaled times will thus vary approximately as the cube root of the body weight, so that 60 min for a 70-kg adult corresponds to 28 min for a 7-kg child.

To clarify the need for scaling the sample times, consider the measurement of GFR, which has units volume/time. Since GFR is a flux, it is proportional to surface area. Since volume is proportional to weight, then for consistency, time must be proportional to weight/area. This makes the scale factors cancel so that the physical relationship is independent of the units of measurement. The result is easily verified in the case of a one-compartment model, since the mean transit time for that case is known to be the volume divided by the flux and is hence proportional to weight/area.

The two-sample method employed a different approach. Solving the four-parameter model when only two plasma measurements are given requires two additional data. For these additional data, we used scaled population "averages" of k_1 and k_2—not the arithmetic mean of individual measurements, but parameters giving the best least-squares fit of calculated to observed ERPF for the patient population as a whole. Since these quantities represent a flux divided by a volume, they were scaled by body surface area divided by body surface area divided by body weight.

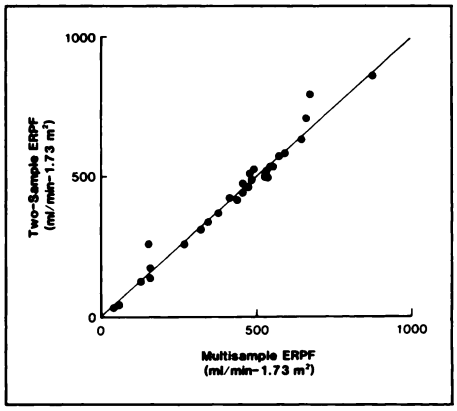

FIGURE 2. OIH clearance (ml/min-1.73 m^2) in children, each calculated from two samples, versus that calculated from the complete clearance curve. The two-sample method was derived solely from OIH clearance data in 68 adults using the two-compartment model (see Appendix). Scaled sample times of 10 and 60 min were used. The line of identity is shown.

RESULTS

The scaled models were tested as follows. First, they were fit to the adult data by least squares. These scaled adult models were then examined to see how well they fit the pediatric data. The results, displayed in Figures 1 and 2, show that the pediatric data could be fit reasonably well using models created from adult data alone. The observed errors were within acceptable limits for clinical use: the residual standard deviation was 67 ml/min for the one-sample method and 36 ml/min for the two-sample method, measured from the line of identity. Scatter around the regression line was even less, with correlation coefficients of 0.966 and 0.987, respectively.

Both pediatric and adult data were then combined and the parameters of the model were recalculated for best fit. Even better fit was obtained by combining the data in this way than by cross-testing pediatric data against the fitted adult model (Figs. 3 and 4).

The calculation was repeated for different sample times, with results summarized in Table 1. Best results for the single-sample method were found when the sample was drawn at a scaled time of 60 min, although timing was not critical and good results were also obtained at 45 or 75 min. These scaled times refer to the standard 70 kg, 1.73 m^2, adult; the actual times of measurement were shorter in children, in proportion to weight/area. For the two-sample method, best results were obtained at scaled times of 10 and 90 min.

With the two-compartment model, the optimum values of k_{10} and k_{20} were both found to be 0.042 min^{-1} for a patient with 1.73 m^2 surface area. (Tauxe (7) obtained values of 0.041 and 0.061 respectively for mean values of

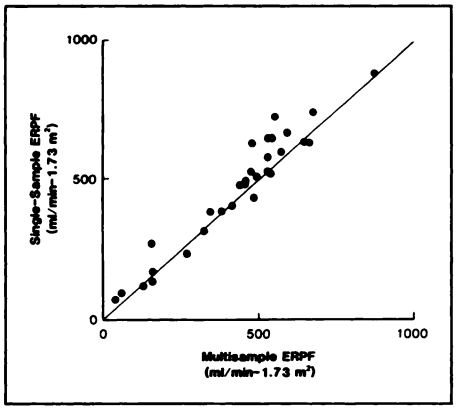

FIGURE 1. OIH clearance (ml/min-1.73 m^2) in children, each calculated from a single sample, versus that calculated from the complete clearance curve. The single-sample method was derived solely from OIH clearance data in 68 adults. The line of identity is shown.

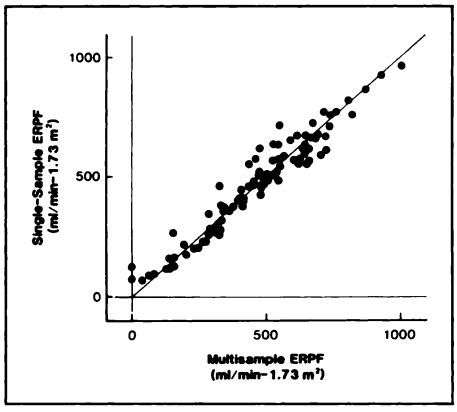

FIGURE 3. OIH clearance (ml/min-1.73 m^2) in 30 children and 68 adults, each calculated from a single sample, versus that calculated from the complete clearance curve. The single-sample method was chosen for best fit to all 98 data. The line of identity is shown.

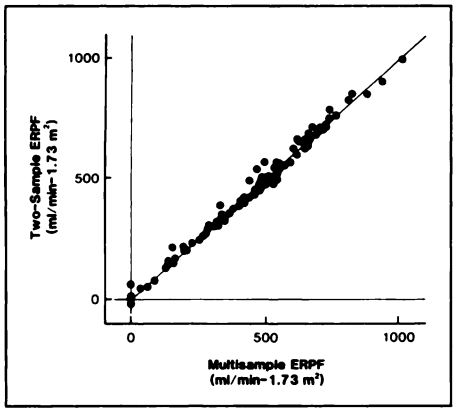

FIGURE 4. OIH clearance (ml/min-1.73 m^2) in 30 children and 68 adults, each calculated from two samples, versus that calculated from the complete clearance curve. The two-sample method was chosen for best fit to all 98 data points and employed the two-compartment model. The line of identity is shown.

these parameters in an adult population, using a different method of calculation.)

DISCUSSION

Since 1966, when Alestig, Hood, and Vikgren showed that GFR could be estimated from a single blood sample drawn 3 hr after a bolus intravenous injection of inulin (*9*), numerous variations on this single-injection single-sample method have been explored, and their clinical value in the adult population has been established (*10*). A variety of agents excreted by glomerular filtration agents have been used to measure GFR, and several agents excreted by tubular-secretion have been used to measure ERPF. The data have been fit to mathematical equations of various form. Sometimes a second blood sample has been used. All methods, however, have depended on first collecting a data base of multi-sample plasma clearance curves and then fitting simplified empirical formulas for clinical use.

Pediatric applications have lagged because of the need for a database of multi-sample plasma clearance curves, and few such studies have been reported. The age range is often incomplete, and confirmation from other centers is lacking. Physiologic scaling reduces the data requirement and can be used to develop pediatric methods from measurements in adults. Pediatric measurements are required to validate the results and to improve the fit, but their number can be minimized.

In principle, any of the published clearance formulas can be scaled; however, they have not been fit so as to minimize the error after scaling, and the sample times used for children for have not often corresponded, after scaling, to those used for adults. In this work, the models have been fit by least squares to scaled data, and measurements were compared at appropriately scaled times.

The present approach should provide a practical framework for developing pediatric methods using new agents such as ^{99}Tc-MAG_3. Although only OIH has been discussed in detail, preliminary results for ^{99}Tc-DTPA are similar (Fig. 5). Since scaled adult formulas work reasonably well for children in the cases of OIH and DTPA, one could expect the same to be true for MAG_3, and the required adult data are available (*13*). However, proper evaluation of such methods will have to await the availability of pediatric multi-sample clearance data. The collection of such data for MAG_3 is under discussion in pediatric nuclear medicine circles both in North America and in Europe.

TABLE 1
Effect of Sampling Time on Error of Measurement (Residual Standard Deviation in ml/min for Combined Data from 30 Children and 68 Adults)

Time (s), min	Method	
	One-sample	Two-sample
45	58.6	
60	54.9	
75	58.1	
10,60		35.4
10,90		27.3
15,90		37.6
15,60		45.4

APPENDIX

For the methods described below, the optimum sample times vary with the height h (cm) and weight w (kg) of the patient and depend on the factor f, where:

$$f = 1.0185\ w^{0.4622}/h^{0.3964}. \qquad \text{Eq. A1}$$

This is based on the surface area formula of Haycock et al. (*14*):

$$\text{area } (m^2) = 0.024265\ H^{0.3964}\ W^{0.5378}$$

and the scaling formula

$$f = (w/70)/(\text{area}/1.73).$$

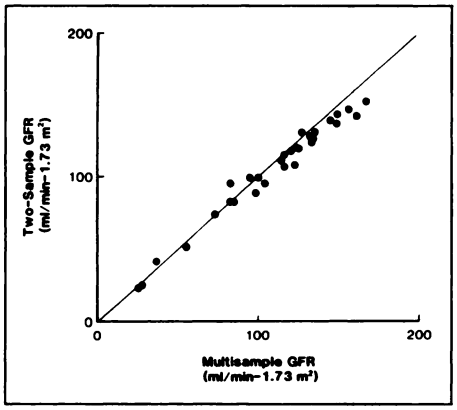

FIGURE 5. Diatrizoate clearance (ml/min-1.73 m^2) in children, each calculated from two samples, versus that calculated from the complete clearance curve. The two-sample method was derived solely from Tc-DTPA clearance data in 40 adults using the two-compartment model (see Appendix). Scaled sample times of 15 and 90 min were used. The line of identity is shown. (Data from references *11* and *12*).

One-Sample Empirical Method

Calculation of ERPF by a single-injection single-sample plasma clearance method using an empirical formula is made as follows:

1. Calculate f from Equation A1 and obtain plasma sample at time t (min) in the interval $45f \le t \le 75f$. The early end of this range is better for patients with good renal function, the later end for patients with poor function.
2. Calculate parameters a and b using the formulas:

$$a = 13.7740 - 0.234133\,(t/f) + 0.00129778\,(t/f)^2$$
$$b = -2.21400e{-}2 + 5.04666e{-}4\,(t/f) - 3.33333e{-}6\,(t/f)^2$$

3. Calculate the scaled ERPF using the formula

$$\text{SCALED ERPF} = a(70/wp) + b(70/wp)^2 \text{ ml/min-1.73m}^2,$$

where p is plasma activity (fraction of administrated dose per liter plasma), h is height (cm), and w is weight (kg).

Sample Calculation

Given an adult patient of height, h, = 183 cm and weight, w, = 82 kg, from Equation A1 we have f = 0.99, so that the plasma sample should be drawn between (45) (0.99) = 44.5 min and (75) (0.99) = 74.2 min. (This calculation will give significantly shorter times for small children).

A blood sample was drawn at 59 min and the count rate for 1 ml of plasma was found to be 4781 cpm. A duplicate of the dose was diluted in two steps to the equivalent of 10 liters, and a 1-ml aliquot counted as standard. The count rate for the standard was 53,621 cpm.

The plasma activity per liter, p, as a fraction of administered dose, was thus:

$$\frac{(4781)(1000)}{(53621)(1000)(10)} = 8.92 \times 10^{-3}.$$

Using the values t = 59 and f = 0.99 in the above equations for a and b,

$$a = 4.43 \text{ and } b = -3.90 \times 10^{-3}.$$

Then substituting a, b, p, and w into the formula for scaled ERPF, one obtains:

$$\begin{aligned}\text{SCALED ERPF} &= 4.43 \times (70/(82 \times 8.92 \times 10^{-3})) \\ &\quad - 3.90 \times 10^{-3} \times (82 \times 8.92 \times 10^{-3})^2 \\ &= 4.43 \times 95.7 - 3.90 \times 10^{-3} \times (95.7)^2 \\ &= 388 \text{ ml/min} - 1.73 \text{ m}^2\end{aligned}$$

Two-Sample Two-Compartment Method

Calculation of ERPF by a single-injection two-sample plasma clearance method using a two-compartment computer model can be made as follows:

1. Calculate f from Equation A1. Obtain two plasma samples, one at 10f–15f min and one at 60f–90f min (preferably near 10f and 90f).
2. Calculate the ERPF by the following algorithm, which will be presented in Pascal-like pseudocode. Notation and theory follow Tauxe (*7*). Briefly, v_1 represents the volume of compartment 1 of a two-compartment model, the compartment into which tracer is directly injected. k_1 and k_2 are fractional intercompartmental rate constants corresponding to Tauxe's $k_{1\text{-}2}$ and $k_{2\text{-}1}$, respectively, where in the Tauxe notation the first number designates the volume of origin and the second the destination. (In Sapirstein's notation (*6*), these are respectively alpha/V_1 and alpha/V_2.) The value of these parameters for a standard 70-kg 1.73-m^2 adult will be designated k10 and k20. Best fit for the combined pediatric and adult populations was found when k10 = 0.042 min^{-1} and k20 = 0.042 min^{-1}. Given these scaled values, to calculate ERPF, first calculate unscaled values of k1 and k2 appropriate for the height and weight of the given patient by using the scale factor t scale: = (ws/70)/(area/1.73); so that

$$k_1\text{: } = k10/\text{tscale}; \quad k_2\text{: } = k20/\text{tscale};$$

The following subprogram, GETCL, based on equations from Tauxe (*7*), calculates as output the parameters c1,c2,l1,l2 of the general two-exponential clearance curve (concentration c versus time t):

$$c = c1 \times \exp(-l1 \times t) + c2 \times \exp(-l2 \times t) \qquad \text{Eq. A2}$$

given as input the ERPF (here designated f3) and the parameters k1, k2, and v1 of the two-compartment model.

```
Procedure GETCL (k1,k2,v1,f3,c1,c2,l1,l2);
begin
    k3: = f3/v1;
    dum: = sqrt (sqr(k1+k3−k2) + 4*k1*k2);
    l2: = (k1+k2+k3−dum)/2;
    l1: = (k1+k2+k3+dum)/2;
    c1: = (k2−l1)/(l2−l1)/v1;
    c2: = (l2−k2)/(l2−l1)/v1;
end {of procedure getcl};
```

Using GETCL and Equation A2, the plasma concentrations at the two sample times can be calculated from trial values of v1 and f3. Newton's method (*15*) can then be used to solve the inverse problem, that of finding those values of v1 and f3 that correspond to the two measured concentrations. The value of f3 computed by Newton's method is the required ERPF.

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