Estimation of Glomerular Filtration Rate in Infants and in Children Using a Single-Plasma Sample Method

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This work was undertaken to look for distribution volume-plasma clearance converting equations(s) that can be used to estimate glomerular filtration rate (GFR) in children. GFR calculated using the two-blood sample slope-intercept method was used for comparison. It was shown that the 2-hr distribution volume and the two-blood sample clearance were closely related. For all the age groups, the coefficient of correlation between these two parameters was high (range: 0.95 to 0.99) and the s.e.e. was low (range 0.76–3.86 ml/min). It was also shown that a linear equation (GFR = 2,602 V_{120} − 0,273) could be used to convert the two hour distribution volume into an accurate estimate of two-blood sample GFR whatever the age of the patient. The use of the single-sample technique for measuring GFR in children is therefore recommendable.

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In the past few decades, a large number of methods for measuring glomerular filtration rate (GFR) have been developed in a relentless search for a more accurate and/or more simplified technique. A single injection method has replaced the constant infusion technique, urine collection is unnecessary, and the number of blood samples required has been reduced to two or less (*1–4*). One of the most attractive methods currently available is the estimation of renal clearance using a single blood sample. This method, also called the volume distribution method, is the least invasive, the easiest to perform, and yields highly accurate results (*4–8*). By choosing an optimal time for blood sampling and by using an adequate converting formula, GFR can be estimated with an error of less than 5 ml/min. Unfortunately, while reports concerning the optimal time and the distribution volume-plasma clearance converting formula are available for adults (*5–8*), very few have been worked out for children (*9–11*). Due to a child's growth rate, there are important variations of anthropometric factors such as height, weight, and biologic factors such as plasma and extracellular volume that may alter the regression formula relating blood activity to renal clearance.

The present retrospective study was undertaken to look for distribution volume-plasma clearance converting equation(s) that can be used to estimate GFR in children of all ages. GFR calculated using the two-blood sample slope-intercept method was used for comparison.

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PATIENTS AND METHODS

Study Design

A retrospective analysis was made on ^{51}Cr-EDTA renal clearance studies routinely performed in the last 3 yr. This yielded a total of 657 GFR measurements fulfilling two criteria: (a) the patients were less than 15 yr old and the first blood sample (see method for ^{51}Cr-EDTA clearance measurement below) was taken between 105 to 135 min after the intravenous injection of the tracer.

These patients were divided into six age groups (Table 1). The limits of each age group were arbitrarily chosen in order to have more than 80 patients in each age class. Each group was then divided randomly into two equal subgroups: a basic subgroup which was used to determine the distribution volume-plasma clearance converting equation, and a test subgroup in which the converting equation determined in the basic subgroup was applied to evaluate its validity.

Two-Blood Sample Slope-Intercept Method

Renal clearance was performed using the one compartment slope-intercept method (*1–2*). Thirty to 100 mCi (depending on the weight of the patients) of ^{51}Cr-EDTA were administered intravenously. The net activity injected to the patient was determined by assaying the syringe containing the dose before and after injection together with an extension tube. Venous blood samples were drawn from the contralateral arm at about 2 and 4 hr postinjection, with exact times being noted.

Renal clearance (ml/min) was calculated from the formula:

$$\text{clearance} = \frac{\text{Dose}\cdot\lambda}{A_{(t)}\cdot e^{(\lambda\cdot t)}}\cdot(0.85), \qquad \text{Eq. 1}$$

where Dose = injected activity (counts$\cdot t^{-1}$), λ = exponential slope of the plasma curve between the two samples (t^{-1}), t = the first plasma sampling time (t), $A_{(t)}$ = plasma activity at time t (counts$\cdot t^{-1}\cdot ml^{-1}$), and $A_{(t)}\cdot e\cdot^{\lambda t}$ = back extrapolation of the plasma disappearance curve to obtain the theoretic initial plasma

TABLE 1
Two-Blood Sample Clearance Values in the Population Studied

Age (yr)	n	Uncorrected for body surface area			Normalized for body surface area = 1.73 m²		
		Mean	s.d.	Range	Mean	s.d.	Range
0.02- 0.99	134	15.4	7.5	3.5- 36.5	78.8	24.1	34.1-130.7
1.0 - 1.99	82	28.7	8.1	9.4- 45.8	101.7	22.4	37.2-148.8
2.0 - 3.99	93	32.9	12.2	14.2- 79.8	97.2	27.7	46.1-155.3
4.0 - 5.99	95	51.4	18.3	14.3-118.7	114.1	32.5	34.4-174.8
6.0 - 9.99	116	67.5	22.3	32.2-139.2	116.5	27.8	61.3-179.3
10.0 -14.99	137	80.8	32.4	10.6-174.7	106.1	32.3	25.0-186.0

tracer concentration (counts·t^{-1}·ml^{-1}). The constant factor 0.85 is the arbitrary correcting factor used to compensate the first exponential component of the plasma disappearance curve neglected in the two blood sample method (*1,8,12*).

Single-Blood Sample Method

The distribution volume (in liter) at time t was defined as

$$V_{(t)} = \frac{\text{Dose}}{A_{(t)}}. \qquad \text{Eq. 2}$$

The 2-hr volume distribution (V_{120}) was therefore given by

$$V_{120} = \frac{\text{Dose}}{A_{120}},$$

where A_{120} corresponds to plasma tracer concentration at the 120th minute after the administration of the tracer. When the blood sample was not taken exactly at the 120th minute, a small correcting factor was introduced:

$$A_{120} = A_{(t)} \cdot e^{(.008)(t-120)},$$

where t was the blood sampling time and $A_{(t)}$ was the plasma concentration at that time. An arbitrary value of 0.008 min^{-1} was employed to replace the biologic decay constant. This value corresponds to the mean value of lambda observed in the population studied.

Distribution Volume-Plasma Clearance Converting Equation

For each age class in the basic group, and for the basic group as a whole, a least squares analysis was performed using the V_{120} as independent variable and two-blood sample slope clearance as dependent variable to produce a regression line. The regression analysis was performed using both the linear and quadratic model. Slope clearance values were taken without adjustment for the patient's height and weight.

The regression equations (linear and quadratic) obtained in the basic groups were then used to convert the 2-hr ^{51}Cr-EDTA distribution volume of the age-related patients in the test group to obtain an estimate of renal clearance. To evaluate the validity of this estimate, linear correlation analysis was performed between this estimate and the corresponding slope clearance.

RESULTS

Table 2 shows the linear and quadratic regression equations obtained in the basic subgroups. A very close relationship was observed between the 2-hr distribution volume and the two-blood sample clearance. For all age groups, the coefficient of correlation was high (range: r = 0.95 to 0.99) and s.e.e. was less than 4 ml/min (range: 0.76 to 3.86 ml/min).

The regression equations obtained in the basic subgroups were used in the age-matched test subgroups to convert the 2-hr distribution volume into an estimate of GFR. In each age class of test subgroup, the linear correlation function relating this parameter and the two-blood sample clearance was close to the identity line with high coefficient of correlation and low s.e.e. (Table 3).

As the converting equations, both linear and quadratic obtained in the various age classes were quite similar

TABLE 2
Relation Between Distribution Volume and Slope Clearance in the Basic Subgroup

Age (yr)	Linear fit*				Quadratic fit†				
	a	b	r	s.e.e.	a	b	c	r	s.e.e.
0.02- 0.99	2.45	0.50	0.98	1.49	−0.07	3.42	−2.11	0.99	1.33
1.00- 1.99	2.59	0.09	0.99	0.76	−0.01	2.82	−1.07	0.99	0.76
2.00- 3.99	2.44	1.73	0.99	1.34	−0.02	3.19	−3.48	0.95	0.97
4.00- 5.99	2.58	0.04	0.99	1.91	−0.01	2.92	−2.88	0.99	1.89
6.00- 9.99	2.22	9.55	0.95	3.75	−0.01	2.97	0.07	0.95	3.60
10.00-14.99	2.62	−0.69	0.99	3.86	−0.00	2.92	−5.07	0.99	3.76
ALL	2.60	−0.27	0.99	3.46	0.00	2.63	−0.48	0.99	3.46

* Linear fit: clearance = $a(VD_t) + b$.
† Quadratic fit: clearance = $a(VD_t)^2 + b(VD_t) + c$.

TABLE 3
Correlation Between Estimate and Slope Clearance in the Test Subgroups

	Using age-specific converting formula			
	Linear		Quadratic	
Age	r	s.e.e.	r	s.e.e.
0.03– 0.99	0.98	1.12	0.98	1.40
1.00– 1.99	0.99	1.28	0.99	0.93
2.00– 3.99	0.99	1.42	0.98	1.04
4.00– 5.99	0.99	1.86	0.99	1.76
6.00– 9.99	0.97	3.21	0.99	3.52
10.00–14.99	0.99	3.76	0.99	3.65

(Table 2), the linear converting equation obtained in the whole basic group (GFR = 2.602 V_{120} − 0.273) was applied to each age class in the test group. The results, presented in Figure 1, indicate that this linear equation can be used to estimate renal clearance accurately in children of all ages including young infants.

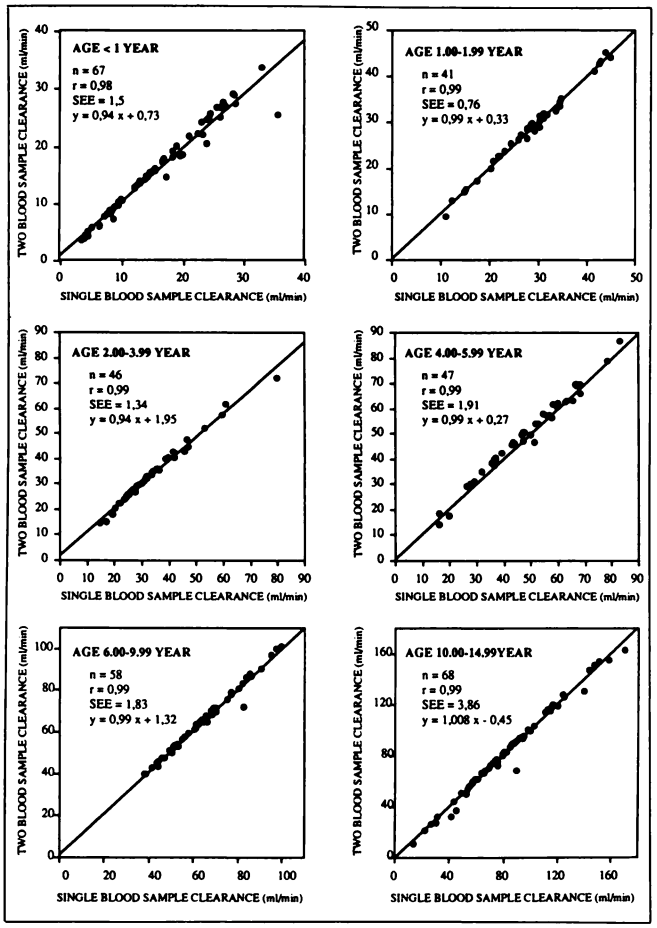

FIGURE 1. Using the linear converting equation obtained from the whole basic group (GFR = 2.602 V_{120} − 0.273), the V_{120} in the test group was converted into an estimate of GFR. Figure 1 shows the correlation between this estimate and the corresponding two-blood sample GFR. For all age groups, the linear correlation function relating this parameter and the two-blood sample clearance was close to the identity line with high coefficient of correlation and low s.e.e.

DISCUSSION

The single injection-single sample method is a simple and accurate method for estimating renal function (*4–10*). First described by Tauxe et al. (*4*) for measuring ERPF, the method has proven equally valid for estimating GFR (*5–8*). In adults and more recently in children, optimal sampling times and various distribution volume-plasma clearance converting formula have been described, but no such data were available for young children or infants. For several reasons, the application of the single plasma sample method in these groups of patients was a priori questionable. It has been demonstrated that the blood sampling time should be adapted to the clearance value and that the overall accuracy of the single sample method is much lower in patients with low GFR. It is well known that GFR in infants and in young children is much lower than in adults (*7,13,14*). Futhermore, remaining activity at a given moment after the administration of a radioactive tracer depends not only on the clearance rate but also on the distribution space of the substance which particularly in fast growing infants varies significantly in function of the age. Using clinical data, Tauxe et al. have shown that in children the optimal sampling time and the converting equation to be employed are not the same as in adults (*9–10*). Because of these backgrounds, the result of the present study was quite unexpected. A linear equation was shown applicable in children of all ages to convert 2-hr distribution volume into an estimate of renal clearance. In adults, the relationship between distribution volume and plasma clearance is generally best described by quadratic, cubic or exponential function. In children, Tauxe et al. (*9–10*) found a linear correlation between these two parameters. Equations 1 and 2 indicate that the function relating the distribution volume at time t and the two-sample slope-intercept clearance is $\lambda \cdot e^{-\lambda \cdot t}$, a complex function with two variables: λ, the biologic decay of the tracer and t, the sampling time (*7,15*). Depending on the values of lambda observed in the population studied and the sampling time chosen, this function can be approximated by various simple functions including cubic, quadratic or linear functions. The results of the present study indicate that in infants and in children with a wide range of renal function, a linear equation can be used to convert the 2-hr distribution volume into an accurate estimate of renal clearance.

It has been reported in adults that single-sample technique is much less accurate for clearance values below 30 ml/min (*7,13,14*). It should be noted however that in adults, such values correspond to low renal function and the exponential slope of plasmatic curve (λ) between 2 and 4 hr is usually less than 0.003/min. In children, up to approximately 4 yr, GFR of 30 ml/min (uncorrected for body surface) is still normal, and the values of λ in these cases are comparable to the normal adults' values. It is therefore obvious that using the 2-hr distribution volume, linear (or quadratic) conversion does not produce a good

estimate of renal clearance in adults with low renal function (low λ values), while it yields an acceptable approximation of this parameter in children with similar absolute clearance values (high λ values). It is however still to be determined whether the single-plasma sample method can be used in children with severe renal failure.

Our choice of the 2-hr distribution volume as parameter was circumstantial. As a retrospective study, only data already available could be used. While it is quite probable that other sampling time could yield even more accurate results, in our opinion the closeness of the relationship between 2-hr distribution volume and slope-intercept clearance observed in this work does not warrant a prospective study, since the population investigated was infants and young children.

For the determination of plasma clearance, the continuous infusion method and single injection with multiple blood sample technique are the two usually accepted reference methods. Unfortunately, these methods are rather unsuitable for routine clinical use in infants and young children. In this study, the reference value for ^{51}Cr-EDTA clearance was calculated from the single exponential derived from the results of blood samples at 2 and 4 hr after injection. Indeed, even if the ^{51}Cr-EDTA in vivo kinetics are much more complex than a single-compartment model, a very close agreement has been repeatedly demonstrated between the two-blood sample technique with the continuous infusion method, multiple blood sampling technique or inulin clearances (*1,2,6,8*).

One may ask whether it is justified, in practice, to use the single-sample technique instead of the well-validated two-sample method. It is obvious that the supplementary data derived from additional blood samples could improve the estimation of renal clearance. However, when dealing with infants and young children, one less blood sample not only saves cost and time but also significantly reduces the physical and psychologic trauma of the patient and parents. Given the accuracy of the single-sample method, the application of this method in children is recommended.

Finally it should be noted that the data presented in this work were based on ^{51}Cr-EDTA. It is still to be demonstrated that the converting equation presented above remains valid when using other glomerular filtration agents (^{99m}Tc-DTPA, ^{125}I-diatrizoate). Given the difference in distribution volume, protein binding, etc. slightly different results could be expected.

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EDITORIAL

Glomerular Filtration Rate in Children: Where We Have Been; Where We Are Going

In this issue of the *Journal*, Drs. Ham and Piepsz present some very encouraging data on the estimation of the glomerular filtration rate (GFR) in children by the use of a single blood sample 2 hr after the administration of ^{51}Cr-EDTA (*1*). Fourteen years ago, these same authors published an appealing method for estimating GFR from the ^{99m}Tc-DTPA renogram (*2, 3*). In these few pages, I would like to review the progress that has been made over the years in the evaluation of renal function with radionuclides, with attention to those considerations which are unique to children.

A major strength of radionuclide examinations of the urinary tract is the evaluation of function. Not only

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