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Feasibility of Estimating Glomerular Filtration Rate in Children Using Single-Sample Adult Technique

Hamphrey R. Ham and Amnon Piepsz
Department of Nuclear Medicine, Saint Pierre Hospital, Free University of Brussels, Brussels, Belgium

This work was undertaken to verify whether a single-sample adult technique, when applied using body surface-corrected plasma concentration, can be used in place of specific pediatric method to estimate ^{51}Cr-EDTA renal clearance in children. **Methods:** In a series of 90 children (aged 0.1 to 15 yr), ^{51}Cr-EDTA renal clearance was calculated using four different approaches. The first approach used specific pediatric single-sample methods; three techniques were chosen and they all used 120-min plasma concentration. The second approach used the same three specific pediatric methods, but they were applied using 120-min plasma concentration prescaled for 1.73 m^2 body surface area. The third approach used single-sample methods designed for adults; three methods were again chosen. They all used 240-min plasma concentration. The fourth approach used the same adults algorithms, but they were applied using 240-min plasma concentration prescaled for 1.73 m^2 body surface area. **Results:** Clearances calculated using the three specific pediatric methods were all closely cross-correlated regardless of whether or not the plasma concentration was prescaled. The use of classical adult methods produced in some cases obviously erroneous clearance values. Improvements were observed when the same adult methods were applied using prescaled plasma concentration. Nonetheless, the clearance values obtained only fairly correlated with those obtained using specific pediatric methods. **Conclusion:** The single-sample adult technique using plasma concentration prescaled for 1.73 m^2 body surface area cannot be used in place of a specific pediatric single-sample method to estimate ^{51}Cr-EDTA renal clearance in children.

Key Words: glomerular filtration rate; single-blood sample method; pediatrics

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The single-sample method is now widely used for estimating renal clearance. Depending on the tracer used, equations have been determined which allow the conversion of a distribution volume at a predetermined time into an estimate of renal clearance (*1–9*). Specific pediatric equations also have been developed (*10–13*). While all these methods give satisfactory results, the requirement of using different methods when dealing with adults or children has motivated the search for an age- independent technique (*14–16*). Within this scope, the approach of Bubeck et al. (*15,16*) was very attractive, especially because of its simplicity. They used ^{99m}Tc-MAG3 (*15,16*) to show that adult formulas can be used in children by scaling down the plasma concentration for body surface areas. They claimed that this principle was applicable for any radiotracer even if, unless we are mistaken, no validation for a glomerular agent has been reported so far.

This work was undertaken to verify whether the single-sample adult technique using plasma concentration prescaled for 1.73 m^2 body surface area could be used in place of a specific pediatric single-sample method to estimate ^{51}Cr-EDTA renal clearance in children.

MATERIALS AND METHODS

Patients

Ninety patients were selected from our single injection (two blood samples) ^{51}Cr-EDTA database (*12*) based on the following criteria: the patient was less than 15 yr old; the first blood sample was taken between 110 and 120 min after intravenous injection of the tracer; and the second blood sample was obtained between 235 and 240 min after tracer administration.

Estimates of Chromium-51-EDTA Clearance

Chromium-51-EDTA renal clearance was estimated using four different approaches. The first used specific pediatric single-sample methods. Three techniques were chosen: (a) Groth and Aasted method (*10*), (b) Tauxe et al. formula (*11*), and (c) Ham and Piepsz converting equation (*12*). All three of these methods used the 120-min plasma concentration. Detailed descriptions of these algorithms are presented in the Appendix. The second approach used the same three specific pediatric methods, but they were applied using the 120-min plasma concentration prescaled for 1.73 m^2 body surface area. The third approach used single-sample methods designed for adults. Three methods were chosen: (a) Morgan et al. converting equation (*2*), (b) Tauxe et al. formula (*3*), and (c) Christensen and Groth method (*5*). These three methods used the 240-min plasma concentration. Detailed descriptions of

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For correspondence contact: H.R. Ham, MD, Department of Nuclear Medicine, Saint Pierre Hospital, Rue Haute 322, 1000 Brussels, Belgium.

TABLE 1
Comparison of Clearances Estimated Using Specific Pediatric Methods

Method	Mean of differences	s.d. of differences
Cross-comparisons between specific pediatric methods		
Groth and Aasted-Tauxe et al.	−0.84	7.34
Groth and Aasted-Ham and Piepsz	1.11	7.39
Tauxe et al.-Ham and Piepsz	1.95	1.53
Comparisons between specific pediatric methods applied using prescaled or unscaled plasma concentration		
Groth and Aasted : prescaled-unscaled	−3.11	4.40
Tauxe et al. : prescaled-unscaled	−0.19	1.91
Ham and Piepsz : prescaled-unscaled	−0.50	0.37

these algorithms are also presented in the Appendix. The fourth approach used the same adult algorithms, but they were applied to the 240-min plasma concentration prescaled for 1.73 m^2 body surface area.

Statistical Analysis

Analysis consisted of comparing the results obtained by the different methods. Pair-wise comparison was performed by calculating the mean of differences to assess bias and the s.d. of differences to assess agreement between the two methods (*17*).

RESULTS

The children selected were aged 0.15–14.93 yr. All age groups were represented (mean = 5.40 yr; s.d. = 4.46 yr). The estimated clearance values ranged from 34 to 186 ml/min/1.73 m^2.

The cross-comparisons between the results obtained by the three specific pediatric methods are presented in Table 1. The three methods were all closely cross-correlated. The s.d. of differences ranged from 1.5 to 7.4 ml/min/1.73 m^2.

When the specific pediatric methods were applied using the 120-min plasma sample prescaled for 1.73 m^2 body surface area, the results were also closely correlated. The s.d. of differences ranged from 1.3 to 8.2 ml/min/1.73 m^2. The results were also closely correlated with those without prescaling (Table 1). For the same method, the s.d. of differences between the results obtained with and without prescaling was less than 5 ml/min/1.73 m^2.

When adult formulas were applied to unscaled plasma concentration, the results varied depending on the method used. Use of the Morgan or Tauxe formula resulted in obviously erroneous clearance values of up to 338 ml/min/1.73 m^2 in some patients.

Use of the Christensen equation resulted in estimated clearances ranging from 33 to 162 ml/min/1.73 m^2, which were similar to those obtained using the specific pediatric methods. On an individual basis, however, some important discordances existed between the results of the Christensen adult formula and those of specific pediatric methods (Fig. 1A).

Improvement was observed when the Morgan and the Tauxe formulas were applied to the body surface area corrected plasma concentration. No more obviously erroneous clearance values were observed. On an individual basis, however, the clearance values obtained were not always close to those obtained using specific pediatric methods. The s.d. of differences ranged from 12.8 to 19.6 ml/min/1.73 m^2 (Table 2).

For the Christensen and Groth adult equation, no improvement was observed when the method was applied using the prescaled plasma concentration (Fig. 1B). The s.d. of differences with the results of Groth and Aasted specific pediatric method was 10.7 ml, when the Christensen and Groth adult method was applied using unscaled plasma concentration, and was 13.3 ml when the method was applied using prescaled plasma concentration.

DISCUSSION

Single Blood Sample Method: Validity and Limitations

When first proposed for measuring OIH clearance by Tauxe et al. in 1971 (*1*), the single blood sample method was viewed skeptically. Indeed, while it is straightforward to deduce that plasma concentration of a renal tracer at different times after intravenous injection is influenced by the level of renal clearance, it is also reasonable to think that the same plasma concentration is also affected by body size. Because people do have different body sizes, plasma concentration could only be loosely related to the renal clearance. Given that the shape of the plasma disappearance curve of a renal tracer is roughly biexponential, for a given tracer, there is an optimal time during which the relation between plasma concentration and renal clearance is close and is only minimally influenced by body size. Therefore, based on plasma concentration at this time, renal clearance can be estimated satisfactorily.

In the last two decades, the validity of Tauxe's approach has been confirmed repeatedly, and the same approach has been extended to other radioactive tracers (*2–8*) and to radiocontrast

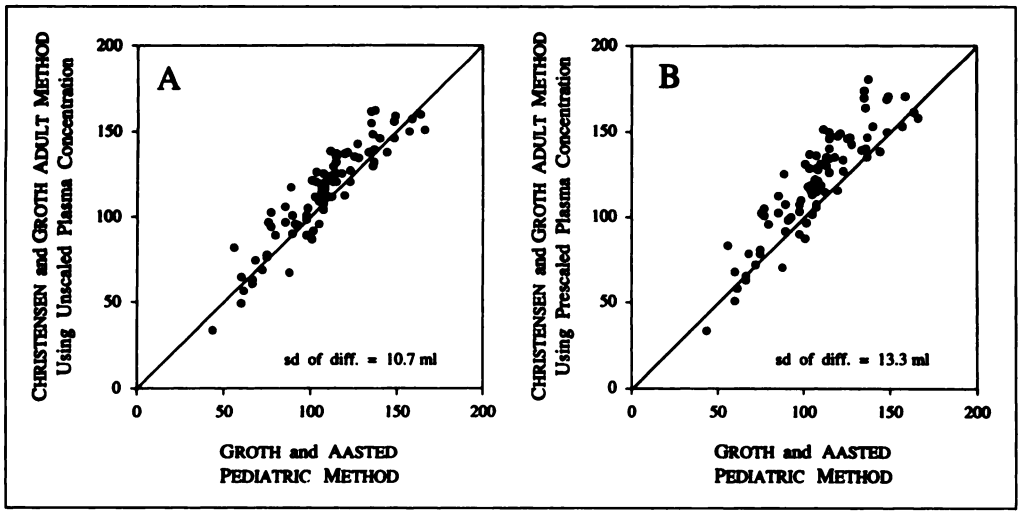

FIGURE 1. Results from an adult method were plotted against results of a specific pediatric method (A). Continuous straight lines correspond to the lines of identity. Fair agreement was observed. The s.d. of differences was 10.7 ml/min/1.73 m^2. No improvement was observed when the same adult method was applied using prescaled plasma concentration (B). The s.d. of differences was 13.3 ml/min/1.73 m^2.

TABLE 2
Comparison of Clearances Estimated by Specific Pediatric Methods Using Unscaled Plasma Concentration and Adult Methods Using Prescaled Plasma Concentration

Pediatric method	Adult method	Mean of differences	s.d. of differences
Groth and Aasted	Morgan et al.	−9.47	16.52
Groth and Aasted	Tauxe et al.	−12.97	13.28
Groth and Aasted	Christensen and Groth	−3.70	12.81
Tauxe et al.	Morgan et al.	−8.63	19.65
Tauxe et al.	Tauxe et al.	−12.14	13.73
Tauxe et al.	Christensen and Groth	−2.86	17.19
Ham and Piepsz	Morgan et al.	−10.58	19.50
Ham and Piepsz	Tauxe et al.	−14.09	13.52
Ham and Piepsz	Christensen and Groth	−4.81	17.16

agents (*18,19*). Specific methods for the pediatric population have also been developed (*9–13*).

Still, the single blood sample method has its limitations. It is inaccurate for estimating reduced renal function (*20,21*). It is purely empirical; therefore, extrapolation to extreme values could result in inconsistencies (*16,22*). The need for different equations when dealing with adults or with children also constitutes a limiting factor, not only in developing a new equation for a new tracer but also when applying an established method in clinical practice (*14–16*). For these reasons, the approach described by Bubeck et al. (*15,16*) is particularly attractive. It is simple because it consists of only scaling down the plasma concentration for a body surface area of 1.73 m^2. It promises an increase in accuracy for low renal function, and some physiologically inconsistent results for extreme values would be corrected. Moreover, the same equation can be used for both children and adults. Bubeck et al. (*15,16*) have shown that the above factor were fulfilled for ^{99m}Tc-MAG3. They claimed that the same principle was applicable for any other tracer, but no data have been presented yet to substantiate it.

Estimation of Chromium-51-EDTA Clearance in Children Using Single-Sample Adult Method

In this work, ^{51}Cr-EDTA renal clearance in a series of children was estimated using specific pediatric methods (*10–12*) and the converting equation developed for adults (*2,3,5*) applied to both body surface corrected and uncorrected plasma concentration.

As expected, close agreement was observed between the results of the three specific pediatric methods, regardless of whether or not the plasma concentration was prescaled. The rather bad results of Morgan and Tauxe adult equations, applied as such to pediatric data, were also not surprising, as they have been designed for adults and not for children. The performance of the Christensen adult formula, on the other hand, was quite interesting. By using this method, no more obviously erroneous results were obtained. It could be due to the fact that in the unscaled Christensen equation there was no constant factor that could be erroneously amplified when the clearance result was normalized to 1.73 m^2 body surface area.

When the Morgan and the Tauxe adult methods were applied to the body surface corrected plasma concentration, they produced results within the expected ranges. Nonetheless, the agreement between the results obtained and those of specific pediatric methods was still not as close as the agreement between specific pediatric methods. The smallest s.d. of differences between a prescaled adult and a specific pediatric method was 12.8 ml/min, whereas the largest s.d. between the differences of two pediatric methods was 7.4 ml/min. Using the Christensen adult method, the prescaling of plasma concentration did not improve the results.

The exact reason why the Bubeck approach works well on MAG3 and not on ^{51}Cr- EDTA is still to be determined. One reason could be the difference in the shape of the plasma disappearance curve. The single-sample method is based on the existence of a time window during which plasma concentration is closely related to the renal clearance. Outside this time window, the plasma concentration is only fairly related to the renal clearance. For ^{99m}Tc-MAG3, the time window is around 40 min for both adults and children (*8,13*). For ^{51}Cr-EDTA, however, the time window in children (between 90 to 120 min) is different from that in adults (between 180 to 300 min) (*2–6,10–12*). In children, the 120-min plasma concentration is closely related to renal clearance. The relationship between the 240-min plasma concentration and renal clearance is, on the other hand, not close enough, precluding its use to estimate ^{51}Cr-EDTA clearance accurately. Prescaling to 1.73 m^2 body surface area of this plasma concentration does not modify this relationship.

The single blood sample method is often criticized for being empirical. The results in this work indicate that a more physiologically tailored approach does not necessarily produce better results. This observation is not unusual in biology and medicine, in which empirical models often perform better than conceptual models because our knowlegde of biological systems is often incomplete. Conceptual models are often incorrect because many important but unknown factors are not included in the model.

CONCLUSION

The results of this work suggest that the single-sample adult technique using body surface corrected plasma concentration cannot be used in place of specific pediatric single-sample methods for the estimation of ^{51}Cr-EDTA renal clearance.

APPENDIX

Methods Used for Estimating Renal Clearance

The following abbreviations were used:

Cl = estimated clearance expressed in ml/min/1.73 m^2.
BSA = body surface area (m^2).
VD_t (l) = distribution volume at time t expressed in liters.
= (administered dose)/(activity in 1 liter of plasma at time t).
VD_t (ml) = distribution volume at time t expressed in milliliters.
= (administered dose)/(activity in 1 milliliter of plasma at time t).
VD_t (l) * BSA = VD_t(l) scaled for body surface area.
= VD_t (l) · (1.73/BSA).
VD_t (ml) * BSA = VD_t(ml) scaled for body surface area.
= VD_t (ml) * (1.73/BSA).

Specific Pediatric Methods Using 120-Minute Sample

Groth and Aasted Method (10):

$$Cl = \frac{-\ln\left[\frac{ECV}{VD_t\,(ml)}\right] \times ECV \times 1.73}{t \times g(t) \times BSA}, \qquad \text{Eq. A1}$$

where t = anytime between 90 to 120 min after injection, ECV = $5867 \times (BSA)^{1.1792}$ and $g(t) = 1.01\ e^{(-0.00011\ t)} + 0.538\ e^{(-0.0178\ t)}$.

Tauxe et al. formula (11):

$$Cl = [1.15 + 2.5\ VD_{120}(l) + 0.0024\ [VC_{120}(l)]^2] \times \frac{1.73}{BSA}. \quad \text{Eq. A2}$$

When the blood sample was not taken exactly at 120 min, a small correcting factor was introduced:

$$A_{120} = A_{(t)} \times e^{(0.008)(t-120)}, \quad \text{Eq. A3}$$

where t was the blood sampling time and A(t) was the plasma concentration at that time. $VD_{120}(l)$ was then calculated using A_{120}.

Ham and Piepsz Converting Equation (12):

$$Cl = [2.602\ VC_{120}(l) - 0.273] \times \frac{1.73}{BSA}. \quad \text{Eq. A4}$$

The same correction as above was performed when the blood sample was not taken exactly at 120 min.

Specific Pediatric Methods Using 120-Minute Sample Scaled for 1.73 m² Body Surface Area

Note: as the plasma concentration was prescaled for BSA = 1.73 m^2, the clearance results were directly expressed in ml/min/1.73 m^2. No further correction was required.

Groth and Aasted Method (10):

$$Cl = \frac{-\ln\left[\frac{ECV}{VD_t \cdot BSA\ (ml)}\right] \times ECV}{t \times g(t)}, \quad \text{Eq. A5}$$

where $ECV = 5867 \times (1.73)^{1.1792}$ and t and g(t) were the same as described above.

Tauxe et al. Formula (11):

$$Cl = 1.15 + 2.5[VC_{120} \times BSA(l)] + 0.0024[VD_{120} \times BSA(l)]^2. \quad \text{Eq. A6}$$

Ham and Piepsz Converting Equation (12):

$$Cl = 2.602[VD_{120} \times BSA(l)] - 0.273. \quad \text{Eq. A7}$$

Adult Formulas Using the 240-Minute Sample:
Morgan et al. Converting Equation (2):

$$Cl = [-7.63 + 1.63[VD_{240}(l)] - 0.0043[VD_{240}(l)]^2] \times \frac{1.73}{BSA}. \quad \text{Eq. A8}$$

When the blood sample was not taken exactly at 240 min, a small correcting factor was introduced:

$$A_{240} = A(t) \times e^{(0.008)(t-240)}, \quad \text{Eq. A9}$$

where t was the blood sampling time and A(t) was the plasma concentration at that time. $VD_{240}(l)$ was then calculated using A_{240}.

Tauxe et al. Formula (3):

$$Cl = \left[138.9\,[1 - e^{[-0.0169(VD240(l)-10.7)]}\right] \times \frac{1.73}{BSA}. \quad \text{Eq. A10}$$

The same correction as above was performed when the blood sample was not taken exactly at 240 min.

Christensen and Groth Method (5):

$$Cl = \frac{-\ln\left[\frac{ECV}{VD_{240}(ml)}\right] \times ECV \times 1.73}{t \times g(t) \times BSA}, \quad \text{Eq. A11}$$

where t = plasma sampling between 180 and 300 min, g(t) = (0.0000017t − 0.0012)(Cl-0.000775t + 1.31) and ECV = 8116.6 (BSA) − 28.2.

Adult Formulae Using the 240-Minute Sample Scaled for 1.73 m² Body Surface Area

Morgan et al. Converting Equation (2):

$$Cl = -7.63 + 1.63\ VD240 \times BSA(l) - 0.0043(VD240 \times BSA(l))^2. \quad \text{Eq. A12}$$

Tauxe et al. Formula (3):

$$Cl = 138.9[1 - e^{[-0.0169(VD240 \times BSA(l) - 10.7]}]. \quad \text{Eq. A13}$$

Christensen and Groth Method (5):

$$Cl = \frac{-\ln\left[\frac{ECV}{VD_{240} \times BSA(ml)}\right] \times ECV}{t \times g(t)}, \quad \text{Eq. A14}$$

where $ECV = 8116.6 \times (1.73) - 28.2$.

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