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Chromium-51-EDTA Clearance in Adults with a Single-Plasma Sample

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In 1996, a committee on renal clearance recommended a mean sojourn time-based methodology for single-sample determination of plasma clearance of ^{99m}Tc-diethylenetriamine pentaacetic acid (DTPA) to be used on adults if the patient's glomerular filtration rate (GFR) is suspected to be >30 ml/min. The main purpose of this study was to derive a mean sojourn time-based formula for calculation of ^{51}Cr-ethylenediamine tetraacetic acid (EDTA) clearance in adults. **Methods:** Two groups of patients with ^{51}Cr-EDTA clearance (Cl) between 16 and 172 ml/min were studied. In Group I (n = 46), reference Cl was determined as a multiplasma sample, single-injection method (Cl_{SM}). Sixteen blood samples were drawn from 0 until 5 hr after a single intravenous injection of ^{51}Cr-EDTA. In Group II (n = 1046), reference Cl was determined by the Brøchner-Mortensen four-sample clearance method (Cl_{BM}). The plasma time-activity curves of Group I were used to derive two mean sojourn time-based formulas (Formulas 1 and 2) for calculation of a single-sample clearance. Formula 1 was derived from the entire time-activity curve, whereas the derivation of Formula 2 used only the final slope of the time-activity curve. The accuracy of the two formulas and the Christensen and Groth ^{99m}Tc-DTPA formula was tested on Group II. **Results:** Chromium-51-EDTA Cl calculated by Formula 1 was almost identical to the Cl calculated by the reference Cl method (r = 0.982; SD_{diff} = 5.82 ml/min). Both ^{51}Cr-EDTA Cl calculated by Formula 2 and by the ^{99m}Tc-DTPA formula showed close correlation with the reference method (r = 0.976, r = 0.985, respectively) but systematically overestimated GFR for the whole range of clearance values by 3.5 and 3.2 ml/min ($p < 0.001$), respectively. **Conclusion:** It is possible to get an accurate determination of ^{51}Cr-EDTA Cl from a single-plasma sample in adults by the mean sojourn time methodology. The determination is marginally more accurate ($p < 0.001$) if using a formula derived from the entire plasma time-activity curve than from only the final slope. The single-sample formula derived for determination of ^{99m}Tc-DTPA Cl tends slightly to overestimate GFR if used to calculate ^{51}Cr-EDTA Cl.

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For the last decade, determination of the glomerular filtration rate (GFR) by single-plasma-sample technology has been increasingly accepted for clinical evaluation of GFR in adults. The first results indicating that it might be possible to determine GFR from the activity in one blood sample were provided by Fischer and Veall (*1*), who used a principle of "apparent volume of distribution" previously introduced by Tauxe et al. (*2*) for calculating effective renal plasma flow as ^{131}I-orthoiodohippuran clearance. In 1981, Groth and Aasted (*3*) presented a nomogram for calculating ^{51}Cr-ethylenediaminetetraacetic acid (EDTA) clearance that preceded the development of a theoretical method for calculating ^{51}Cr-EDTA clearance from a single-plasma sample in children on the basis of the mean sojourn time of ^{51}Cr-EDTA in its distribution volume (*4*). Today, numerous methodologies for calculation of single-sample GFR are available, and several of these have been compared by independent studies (*5–10*).

In 1996, a committee on renal clearance (*11*) recommended the mean sojourn time-based methodology applied for single-sample determination of plasma clearance of ^{99m}Tc-diethylenetriamine pentaacetic acid (DTPA) by Christensen and Groth (*12*) to be used on adults if the patient's GFR was suspected to be more than 30 ml/min. It also acknowledged that ^{51}Cr-EDTA is an acceptable alternative agent to ^{99m}Tc-DTPA. Indeed, determining GFR by using ^{51}Cr-EDTA, instead of ^{99m}Tc-DTPA, remains the approach chosen by many laboratories in the world. The Christensen and Groth formula, however, has never been standardized for ^{51}Cr-EDTA. Therefore, it is desirable that the mean sojourn time-based methodology also be developed to measure ^{51}Cr-EDTA clearance in adults.

The purpose of this study was to use the single-plasma

sample approach, as used to derive a formula for determining ^{99m}Tc-DTPA single-sample clearance by the Christensen and Groth formula, to derive a formula for calculating ^{51}Cr-EDTA clearance in adults. In addition, we wanted to compare whether such a formula had the same accuracy regardless of whether it was derived from clearance as calculated from the entire plasma time-activity curve or by only a one-pool approach from the final slope of the plasma time-activity curve, as defined from a few plasma samples (*13*). Finally, we wanted to investigate whether the single-sample formula derived for ^{99m}Tc-DTPA clearance can be safely used for calculating ^{51}Cr-EDTA clearance.

MATERIALS AND METHODS

Patients

Patients were separated into two groups. Group I contained 46 patients with clearance values >15 ml/min referred for determination of ^{51}Cr-EDTA clearance. The patients were examined at the Department of Clinical Physiology and Nuclear Medicine, Skejby University Hospital, Aarhus, Denmark. None of the patients had edema, ascites or renovascular hypertension.

Group II contained 1046 consecutive patients referred for routine determination of ^{51}Cr-EDTA clearance by Brøchner-Mortensen's method at the Department of Clinical Physiology, Norrlands University Hospital, Umeå, Sweden. These patients were not prospectively examined for edema, ascites or renovascular hypertension.

The results of Group I were used to derive a single-plasma-sample method by the approach previously described for ^{99m}Tc-DTPA from the entire plasma time-activity curve (Formula 1) and the final slope (Brøchner-Mortensen) only (Formula 2). The accuracy of the resulting formulas along with the previously published formula for determination of ^{99m}Tc-DTPA clearance (*12*) were tested on Group II.

Procedure

Group I. The patients were confined to bed throughout the examination, which lasted 5 hr. A Viggo Venflon (Viggo BOC Ohmeda Ltd., Helsingborg, Sweden) for tracer injection and blood sampling was inserted into a cubital vein. A bolus injection of 4 MBq ^{51}Cr-EDTA in 5 ml 0.9% NaCl solution was given through the Venflon. The Venflon was then flushed with a minimum of 10 ml 0.9% saline. Blood samples of 5 ml were drawn 1 min before the injection and 2, 5, 10, 20, 30, 40, 60, 75, 90, 120, 150, 180, 210, 240, 270 and 300 min after the injection.

Group II. The patients were allowed to move around from the time of injection of ^{51}Cr-EDTA until blood sampling started. A single injection of 3.7 MBq ^{51}Cr-EDTA was given intravenously. The venflon was flushed with a minimum of 10 ml 0.9% saline. Blood samples were drawn 180, 210, 240 and 270 min after injection.

The radioisotope activity was counted in plasma samples of 2 ml together with precisely determined plasma blanks and a standard dilution of the injectate in a scintillation detector for up to 20 min or to a statistical counting error of <1%.

Calculations

Group I. Clearance was determined from the entire plasma time-activity curve, as defined by all the plasma samples. The results thus calculated are referred to as the standard method results, Cl_{SM} (*14*).

Clearance was also determined by the one-pool model of Brøchner-Mortensen (*13*), Cl_{BM}, using the final slope of the plasma elimination curve of ^{51}Cr-EDTA, as defined by the activity in the 180-, 210-, 240-, 270- and 300-min plasma samples.

The extracellular volume (ECV), defined as the ^{51}Cr-EDTA distribution volume, was determined from the entire plasma time-activity curve according to Sapirstein et al. (*14*), ECV_{SM}, and from the one-pool approach of Brøchner-Mortensen, ECV_{BM} (*15*).

The body surface area (BSA) was calculated according to Haycock et al. (*16*) and was used to establish an empirical relationship between ECV (ECV_{SM} and ECV_{BM}) and BSA [ECV = f(BSA)].

To derive the single-sample formula by means of the mean sojourn time principle, the mean sojourn time, $\bar{t}$, for ^{51}Cr-EDTA's sojourn in ECV was calculated using the standard method values as $\bar{t}_{SM}$, where $\bar{t}_{SM} = ECV_{SM}/Cl_{SM}$ and using the values calculated according to Brøchner-Mortensen, $\bar{t}_{BM}$, as $\bar{t}_{BM} = ECV_{BM}/Cl_{BM}$ (*4*).

The fractions $s_{SM}(t)/(1/\bar{t}_{SM})$ and $s_{BM}(t)/(1/\bar{t}_{BM})$ were calculated for t = 180, 210, 240, 270 and 300 min where:

$$s_{SM}(t) = \frac{-\ln\left[C(t)\dfrac{ECV_{SM}}{Q_0}\right]}{t}$$

and

$$s_{BM}(t) = \frac{-\ln\left[C(t)\dfrac{ECV_{BM}}{Q_0}\right]}{t}.$$

The functions $g_{SM}(t)$ and $g_{BM}(t)$ were determined by performing a regression analysis of $s_{SM}(t)/(1/\bar{t}_{SM})$ and $s_{BM}(t)/(1/\bar{t}_{BM})$ on t (*4*).

Finally, the derived relations using the standard method were inserted in the general formula for calculating single-sample clearance by the mean sojourn time approach (the Formula 1 approach) as:

$$Cl_{S\text{-}SM} = \frac{-\ln\left[C(t)\dfrac{ECV_{SM}}{Q_0}\right]ECV_{SM}}{t \times g_{SM}(t)}. \qquad \text{Eq. 1}$$

The derived relations using the Brøchner-Mortensen method were tested in the same general formula (the Formula 2 approach) as

$$Cl_{S\text{-}BM} = \frac{-\ln\left[C(t)\dfrac{ECV_{BM}}{Q_0}\right]ECV_{BM}}{t \times g_{BM}(t)}. \qquad \text{Eq. 2}$$

Group II. The radioactivity in the four plasma samples were used to calculate Cl_{BM} (*13*). The accuracy of the formulas derived from Group I (Formula 1 and Formula 2) together with the formula derived from ^{99m}Tc-DTPA by Christensen and Groth (*12*) were tested on Group II, using Cl_{BM} as a reference method.

Statistical Analysis

Regression analysis was performed by means of the least squares method. The Student's t-test was applied to the intercepts and slopes of the regression lines. The s.d. of y on x, $SD_{y/x}$, was determined. Comparison between multisample clearances, Cl_{SM} (Cl_{SM} = Cl_{SM} or Cl_{BM}), and single-sample clearances, Cl_S, was performed by determining the s.d. of the difference between Cl_{SM} and Cl_S, SD_{diff} (*17*). The Wilcoxon matched-pairs test was used to identify any difference in accuracy of the clearance values calculated as $Cl_{S\text{-}SM}$, $Cl_{S\text{-}BM}$, Cl_{BM} and Cl_{Tc}. In figures in which confidence limits are shown, the 0.95 level is used. Significance was reached when $p < 0.05$ was obtained.

RESULTS

The composition of Group I with respect to sex, age, BSA and clearance is shown in Table 1.

TABLE 1
Composition of Group I (18 Women and 28 Men) with Regard to Age, Body Surface Area and ^{51}Cr-EDTA clearance

								Total
Age (yr)	Range	20–29	30–39	40–49	50–59	60–69	70–79	20–79
	Mean	24.5	35.3	46.0	54.9	64.9	71.3	51.4
Body surface area (m^2)	Range	1.53–2.31	1.92–2.60	1.63–2.30	1.49–2.27	1.65–2.01	1.63–2.07	1.49–2.60
	Mean	1.82	2.13	1.90	1.96	1.85	1.85	1.93
Clearance (Cl_{SM}) (ml/min)	Range	53–110	18–107	26–107	19–104	18–66	16–59	16–110
	Mean	81	66	69	60	41	38	58
No. of patients		4	7	8	14	7	6	46

EDTA = ethylenediaminetetraacetic acid.

The correlation between ECV_{SM} and BSA (Fig. 1A) and the correlation between ECV_{BM} and BSA (Fig. 1B) were significant ($r = 0.81$, $p < 0.001$ and $r = 0.83$, $p < 0.001$). The functions ECV = f(BSA) were:

$$ECV_{SM} = 10800 \times BSA - 5578.6 \ (SD_{y/x} = 1915 \text{ ml}) \quad \text{Eq. 3}$$

and,

$$ECV_{BM} = 11476 \times BSA - 7320.9 \ (SD_{y/x} = 1838 \text{ ml}). \quad \text{Eq. 4}$$

The regression lines for ECV_{SM} and ECV_{BM} on BSA did not differ significantly from each other.

The regression analysis of $s_{SM}](t)/(1/\bar{t}_{SM})$(Fig. 2) and $s_{BM}](t)/(1/\bar{t}_{BM})$ at t = 180, 210, 240, 270, and 300 min had the smallest residual variance when biexponential fits were applied. The g(t) functions were determined as:

$$g_{SM}(t) = 0.324 \times e^{-0.0121 \times t} + 1.13 \times e^{-0.000289 \times t} \quad \text{Eq. 5}$$

and

$$g_{BM}(t) = 1.27 \times e^{-0.000645 \times t} - 0.0966 \times e^{-0.162 \times t}. \quad \text{Eq. 6}$$

Inspection of the data showed that there was an over-representation of low clearance values among high $s(t)/(1/\bar{t})$ values, whereas high clearance values were over-represented among low $s(t)/(1/\bar{t})$ values.

To analyze the extent of the relation a regression analysis of $s_{SM}(t)/(1/\bar{t}_{SM})$ on Cl_{SM} and $s_{BM}(t)/(1/\bar{t}_{BM})$ on Cl_{BM} for t = 180, 210, 240, 270 and 300 min was performed (Table 2). The correlation between $s_{SM}(t)/(1/\bar{t}_{SM})$ and Cl_{SM} was closer at 300 min than at 180 min after the injection. The relationship between $s_{BM}(t)/(1/\bar{t}_{BM})$ and Cl_{BM} was almost the same for the entire time interval. Moreover, $s(t)/(1/\bar{t})$ was more closely related to Cl when calculated as $s_{BM}(t)/(1/\bar{t}_{BM})$ than when calculated as $s_{SM}(t)/(1/\bar{t}_{SM})$.

To take advantage of the relationship between g(t) and Cl, the regression lines were combined to yield two new g(t) functions, $g_{SM}(t)_{corr}$ and $g_{BM}(t)_{corr}$ as

$$g_{SM}(t)_{corr} = (-4.18 \times 10^{-6} \times t + 6.43 \times 10^{-4})Cl + 1.60 \times 10^{-6} \times t^2 - 0.00103 \times t + 1.25. \quad \text{Eq. 7}$$

$$g_{BM}(t)_{corr} = (-1.30 \times 10^{-6} \times t - 1.19 \times 10^{-3})Cl + 3.00 \times 10^{-6} \times t^2 - 0.00206 \times t + 1.49. \quad \text{Eq. 8}$$

The $g_{SM}(t)_{corr}$ and ECV_{SM} were then inserted in Eq. 1 allowing Cl_{S-SM} to be calculated by an iterative procedure as:

$$Cl_{S-SM(-n)} = \frac{-\ln\left[\frac{C(t) \times ECV_{SM}}{Q_0}\right] \times ECV_{SM}}{t \times g_{SM}(t)_{corr}(n-1)}, \quad \text{Eq. 9}$$

where $g_{SM}(t)_{corr}$ $(n-1)$ is found by insertion of Cl_{n-1} into Equation 7, and $Cl_{S-SM(n+n-1)}$ is found by using $g_{SM}(t)$ from Equation 5. The analog equation for calculation of single sample clearance by the equation derived from Brøchner-Mortensen's method, Cl_{S-BM}, was:

$$Cl_{S-BM(-n)} = \frac{-\ln\left[\frac{C(t) \times ECV_{BM}}{Q_0}\right] \times ECV_{BM}}{t \times g_{BM}(t)_{corr}(n-1)}. \quad \text{Eq. 10}$$

Figure 3 shows a comparison between Cl_{SM} and Cl_{S-SM}, for t = 300 min (A) and Cl_{SM} and Cl_{BM} (B). The correlation was close ($r = 0.994$, $p < 0.001$ and $r = 0.997$, $p < 0.001$) and did not differ significantly from the lines of identity. The difference between the Cl_{BM} values and the Cl_{SM} values ($Cl_{BM} - Cl_{SM}$),

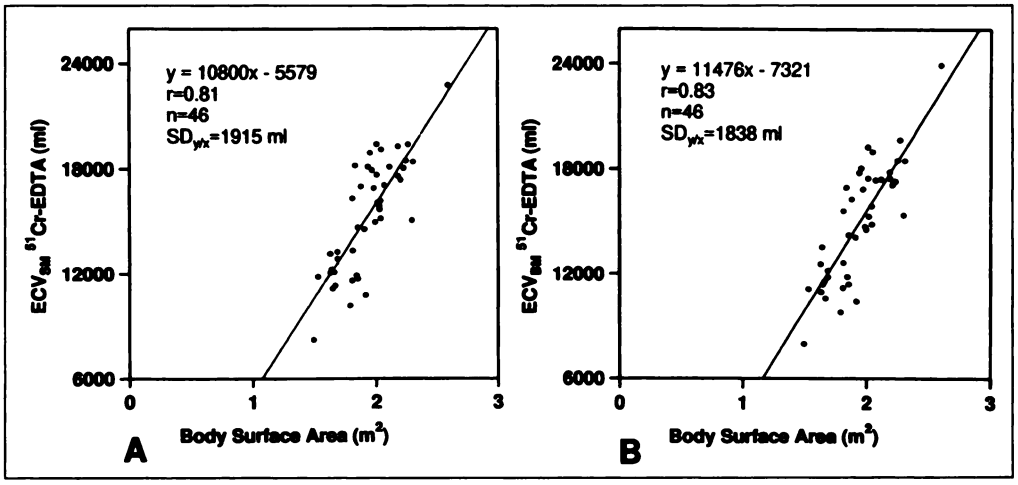

FIGURE 1. The correlation between (A) ECV_{SM} and (B) ECV_{BM} and body surface area.

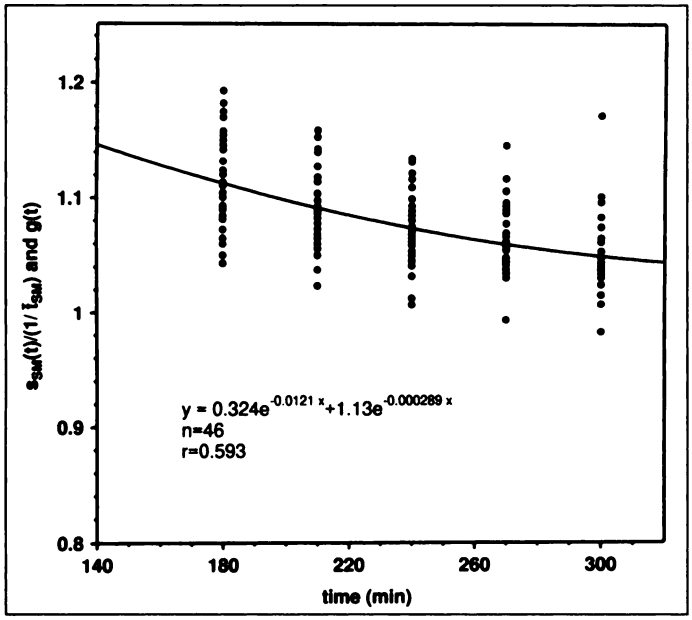

FIGURE 2. Equation $s_{SM}(t)/(1/\bar{t}_{SM})(\cdot)$ for t = 180, 210, 240, 270 and 300 min, g(t) (—) describes the relationship between $s_{SM}(t)/(1/\bar{t}_{SM})$ and time.

however, was significantly smaller than the difference between the Cl_{S-SM} and Cl_{SM} values ($p < 0.05$).

The results of comparing Cl_{S-SM} and Cl_{S-BM} (for t = 300 min) to the material from which they were derived showed that there was no difference between their accuracy (Wilcoxon).

The composition of Group II with respect to age, body surface and clearance, determined according to Brøchner-Mortensen (*13*) is shown in Table 3.

The testing of the two formulas (Eqs. 9 and 10) was made on Group II along with the single-sample clearance method derived from ^{99m}Tc-DTPA (Cl_{Tc}) by Christensen and Groth.

The results of the regression analysis of Cl_{S-SM}, Cl_{S-BM} and Cl_{Tc} on Cl_{BM} for t = 180 and 270 min are shown in Figure 4. The correlation coefficient for Cl_{S-SM} on Cl_{BM} was r = 0.982 for t = 180 min (Fig. 4A) and r = 0.979 for t = 270 min (Fig. 4B). The corresponding correlation coefficients for Cl_{S-BM} and Cl_{Tc} on Cl_{BM} were r = 0.976 and r = 0.985 for t = 180 min and r = 0.970 and r = 0.984 for t = 270 min.

In Figure 5, the difference between Cl_{BM} and Cl_{S-SM} (Fig. 5A) and the difference between Cl_{BM} and Cl_{Tc} (Fig. 5B), for t = 180 min, were compared with reference to Cl_{BM}. For $Cl_{BM}-Cl_{S-SM}$, there was a uniform scatter of the results around the zero-line (coefficient of variation, CV = 5.5%). There was only a small, but significant, overestimation of GFR for the whole range of clearance values by 1.5 ml/min ($p < 0.001$). This was even more pronounced in the case for $Cl_{BM}-Cl_{Tc}$ in which there was a systematic overweight of results below the zero-line (CV = 6.5%) that resulted in an overestimation of GFR by 3.2 ml/min ($p < 0.001$). The analog comparison between $Cl_{BM}-Cl_{S-BM}$ and Cl_{BM} showed that Formula 2 overestimated GFR by 3.5 ml/min ($p < 0.001$).

DISCUSSION

The results of this study show that it is possible to get an accurate determination of ^{51}Cr-EDTA clearance from a single plasma sample in adults by applying the mean sojourn time-based approach previously shown to be very precise for determination of ^{99m}Tc-DTPA plasma clearance from the activity in a single plasma sample.

The precise calculation of plasma clearance of ^{51}Cr-EDTA by this approach relies on a determination of two points where a virtual monoexponential elimination curve intersects the real plasma time-activity curve. The first value is given by Q_0/ECV (at t = 0). The second reference value is found at $t = \bar{t}$ (*4*).

To derive the method, it was a prerequisite that ECV, as defined as the distribution space of ^{51}Cr-EDTA, could be estimated from BSA and that a function, g(t), could be determined that corrects for the fact that it cannot be known in advance when the real and the virtual time-activity curves will intersect at $t = \bar{t}$ (*4*).

The correlation between the distribution volume of ^{51}Cr-EDTA (ECV_{BM}), as calculated from the final slope of the plasma time-activity curve and BSA (r = 0.83), was almost identical to the correlation between ECV_{SM} and BSA (r = 0.81). Even if the determination of ECV by the simplified method of Brøchner-Mortensen is not as accurate as the determination of ECV from the entire plasma time-activity curve (*15*), apparently the estimation of ECV_{BM} from BSA was not affected.

Surprisingly, the correlation between the distribution volume of ^{51}Cr-EDTA (ECV_{SM}) and BSA (r = 0.81) was much closer than has previously been reported between the ^{99m}Tc-DTPA distribution space and BSA (r = 0.35) by Christensen and Groth in 1986 (*12*). This difference may be related to the slightly different physical and/or chemical properties of EDTA and DTPA. EDTA (292 daltons) is a slightly smaller molecule than DTPA (393 daltons). Smaller molecules expectedly should have a larger distribution space than larger molecules, even when the distribution volumes of the molecules in question are all contained in the extracellular space (*18*). We found, how-

TABLE 2
Regression Analysis of $s_{SM}(t)/(1/\bar{t}_{SM})$ on Cl_{SM} (upper part) and $s_{BM}(t)/(1/\bar{t}_{BM})$ on Cl_{BM} (lower part) for Different Values of Time

	$\frac{s(t_{180})}{(1/t)}$	$\frac{s(t_{210})}{(1/t)}$	$\frac{s(t_{240})}{(1/t)}$	$\frac{s(t_{270})}{(1/t)}$	$\frac{s(t_{300})}{(1/t)}$
Intercept	1.118	1.106	1.094	1.089	1.083
Slope × 10^{-4}	−0.82	−2.7	−3.6	−4.8	−6.1
r^2	0.004	0.074	0.147	0.274	0.365
p <	–	–	0.01	0.001	0.001
Intercept	1.212	1.186	1.163	1.149	1.138
Slope × 10^{-4}	−14.2	−14.9	−14.7	−15.2	−16.0
r^2	0.451	0.552	0.566	0.595	0.617
p <	0.001	0.001	0.001	0.001	0.001

– = Not significant.

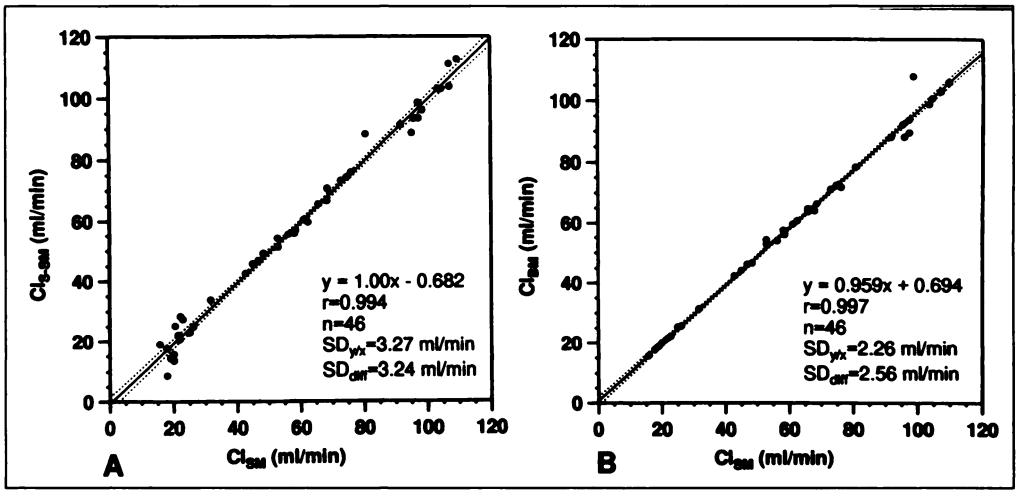

FIGURE 3. (A) Cl_{S-SM} and (B) Cl_{BM} compared with standard multiple sample method, Cl_{SM}. Interrupted lines indicate confidence interval of regression line.

ever, that for individuals with a BSA smaller than 2.07 m^2 (76% of the patients of Group I), their estimated EDTA distribution spaces were systematically smaller when calculated by Equations 3 or 4 than from the DTPA-based regression equation of Christensen and Groth. ^{99m}Tc-DTPA has been reported to bind to plasma proteins to a varying degree (*19–22*), whereas plasma protein binding of ^{51}Cr-EDTA seems to be considerably smaller (*23*). Variable differences in plasma protein binding may explain the difference in calculated distribution space and coefficient of correlation.

The significant correlation between $s(t)/(1/\bar{t})$ and time made it possible to establish the g(t) function. The range of $s(t)/(1/\bar{t})$ values between the confidence limits of the function was quite narrow indicating that great adjustments were not needed to correct for the fact that the plasma sample is only rarely drawn at $t = \bar{t}$.

The sloping of the g(t) function was somewhat steeper for low values of time as opposed to high values where g(t) assumed a rather constant level. This implies that the magnitude of correction necessary for the calculation of a precise Cl_S value does not increase very much after a certain period of time.

The scatter of the values around the g(t) function was not random but related to clearance for the investigated interval of time, $180 < t < 300$ min. It was possible to build this dependency into an improved g(t) function, $g(t)_{corr}$ and, thereby, get a further reduction of the variance thus providing a better overall basis for a precise determination of clearance by an iterative process.

The slopes of the functions resulting from the regression analysis of $s(t_{180-300})/(1/\bar{t})$ on clearance were slightly greater if the $s(t)/(1/\bar{t})$ values were derived from the final slope than if the entire plasma time-activity curve was used (Table 2). This suggests that the $g(t)_{corr}$ function might correct more effectively in Formula 2 than in Formula 1. This difference was greatest early in the time-interval 180–300 min, where the dependence of $s(t)/(1/\bar{t})$ on Cl_{SM} was significantly smaller (or even insignificant) than for later times. However, for time values greater than 270 min the difference was minimal.

The clearance values, Cl_{S-SM} and Cl_{S-BM}, calculated according to Formulas 1 and 2 (for t = 300 min), proved to be almost identical to Cl_{SM} when tested on Group I ($r = 0.994$ and $r = 0.993$). Therefore, it appeared as if there was no reduction in accuracy when deriving the one-sample method from the final slope of the time-activity curve, which was the case for Formula 2. The accuracy of Formula 2, of course, is not only related to the precision of Cl_{BM}, which was very precise, but also to the fact that the correlation between ECV_{BM} and BSA ($r = 0.83$) was almost identical to the correlation between ECV_{SM} and BSA ($r = 0.81$). Another explanation for the precision may be that the correcting properties of the $g(t)_{corr}$ function compensate for minor differences between Cl_{BM} and Cl_{SM}. In fact, the correlation between Cl_{S-SM} and Cl_{SM} ($r = 0.994$) was only insignificantly smaller than between Cl_{BM} and Cl_{SM} ($r = 0.997$), and nearly all the results lay very close to the line of identity. The SD_{diff} of Cl_{S-SM} on Cl_{SM} ($SD_{diff} = 3.24$ ml/min) was slightly, but insignificantly, larger ($p < 0.06$) than the SD_{diff} of Cl_{BM} on Cl_{SM} ($SD_{diff} = 2.56$ ml/min).

Due to the excellent accuracy of Cl_{BM} with reference to Cl_{SM} we considered it justified to use Cl_{BM} as a reference method when comparing different single-sample clearance methods on Group II, in spite of the fact that Cl_{BM} does itself arise from a slightly simplified method.

The results of comparing Cl_{S-SM} and Cl_{BM} of the 1046 patients of the test material of Group II confirmed the precision of Formula 1. There was only a minor deviation of the regression line ($y = 1.00x + 1.30$ for $t = 180$ min) with respect to the line of identity ($y = x$). When testing Formula 2, the deviation of the regression line from the line of identity was

TABLE 3
Composition of Group II with Regard to Age, Body Surface Area and ^{51}Cr-EDTA Clearance

								Total
Age (yr)	Range	16–29	30–39	40–49	50–59	60–69	70–85	16–85
	Mean	22.0	35.6	45.5	54.9	65.3	74.3	52.4
Body surface area (m^2)	Range	1.37–2.32	1.37–2.59	1.37–2.59	1.34–2.52	1.32–2.49	1.34–2.30	1.32–2.59
	Mean	1.81	1.83	1.93	1.89	1.87	1.80	1.86
Clearance (Cl_{SM}) (ml/min)	Range	33–164	19–146	18–171	21–172	21–119	20–132	18–172
	Mean	102	83	84	75	62	51	74
No. of patients		115	136	186	233	199	177	1046

EDTA = ethylenediaminetetraacetic acid.

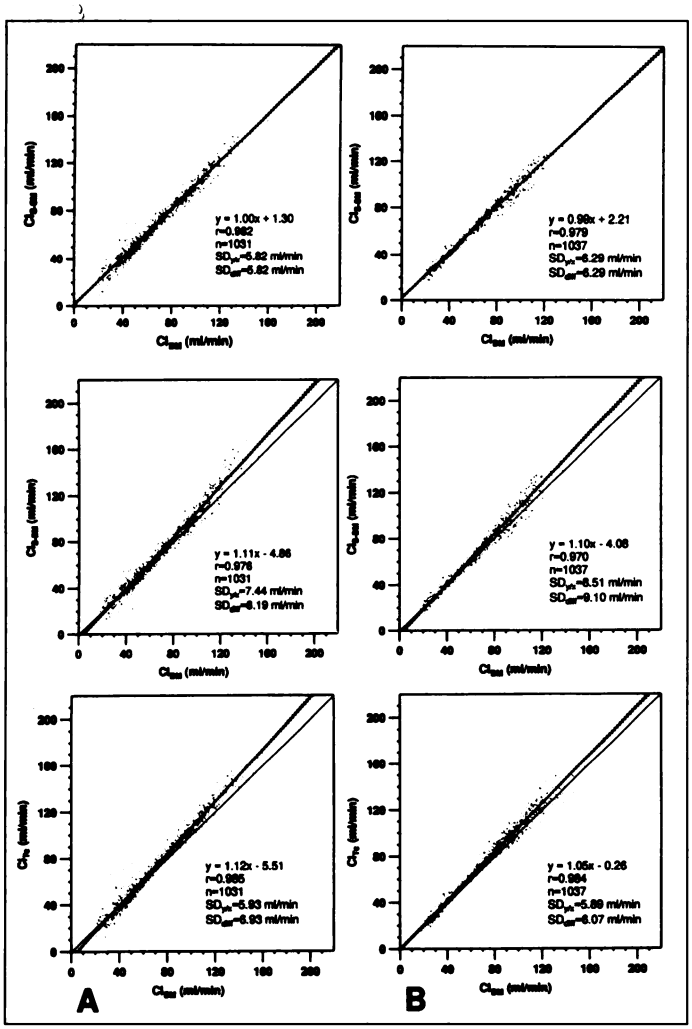

FIGURE 4. Regression analysis for Cl_{S-SM} on Cl_{BM} (upper panel), Cl_{S-BM} on Cl_{BM} (middle panel) and Cl_{Tc} on Cl_{BM} (lower panel) for (A) t = 180 min and (B) t = 270 min, respectively. Regression lines, confidence intervals (interrupted lines) and lines of identity are shown.

somewhat greater ($p < 0.01$). This indicates that when deriving a formula from a method that has already been simplified, some of the precision which has been offered for the sake of precision by simplification of the first method, though minimal, may be transferred and increased to reduce the precision of the yet further simplified method. In the case of Brøchner-Mortensen's method, though simplified, it is still so precise that it took 1046 patients to reveal that deriving a one-sample formula from this method is marginally less accurate than when deriving it from the whole-plasma curve. There was a systematic, but small, overestimation of ^{51}Cr-EDTA clearance for the whole range of clearance values if the single-sample formula derived for ^{99m}Tc-DTPA was used. Although the clinical implication of this difference may be limited, it clearly illustrates the potential danger of employing the regression coefficients derived for one radiopharmaceutical on another.

Surprisingly, the correlation between Cl_S and Cl_{BM} was closer when the plasma sample was drawn after 180 min than if it was drawn after 270 min, regardless of choice of formula. The differences were small and mostly pertained to clearance values >80 ml/min. For lower clearance values (<80 ml/min), the individual results of the curves were closer to the regression line if the plasma sample was drawn after 270 min than after 180 min. This phenomenon probably relates to the correcting properties of the g(t) function. The g(t) function corrects for untimely drawing of the blood sample with respect to the mean sojourn time. The mean sojourn time for ^{51}Cr-EDTA in ECV in patients with clearance values >80 ml/min is generally not very different from a value of 180 min, whereas the mean sojourn time for patients with clearance values <80 ml/min is often closer to 270 min or even longer. The smaller the need to be corrected by the g(t) function, the more precise the clearance value.

When testing the single-plasma sample formulas on the 1046 patients of Group II (for t = 180 min), 14 results were obviously outliers regardless of the single-plasma sample formula being chosen. In 13 of them, the patients' records showed that the patients had edema or severe electrolyte derangement at the time of their examination. All these patients also had moderate to advanced insufficiency of the kidneys. Patients with edema and electrolyte imbalance do not fulfill the prerequisites of using plasma clearance of ^{51}Cr-EDTA as an index of GFR, since they do not consistently have a close correlation between plasma clearance and renal clearance of ^{51}Cr-EDTA (*24*). When determining GFR as the plasma clearance of ^{51}Cr-EDTA, particular attention should be paid to this source of error before injecting the bolus into the patient.

The 13 outliers were removed, and Formula 1 was again tested against Cl_{BM} on the remaining 1018 patients of the final test group (for t = 180 min). This procedure significantly improved the SD_{diff}, going from 5.82 to 5.02 ml/min ($p < 0.001$).

CONCLUSION

It was possible to get an accurate determination of ^{51}Cr-EDTA clearance from a single-plasma sample in adults by applying the mean sojourn time-based approach previously

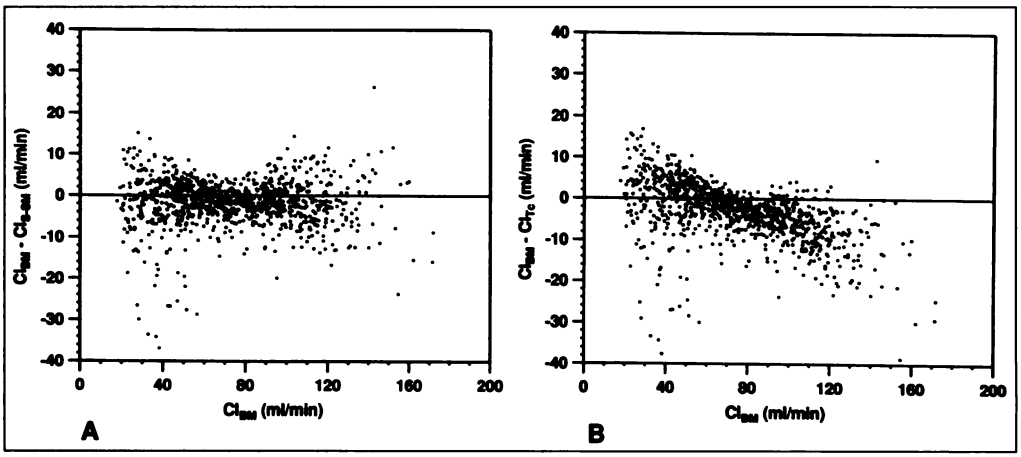

FIGURE 5. Difference between Cl_{BM} and Cl_{S-SM} compared with (A) Cl_{BM} and difference between Cl_{BM} and Cl_{Tc} compared with (B) Cl_{BM}.

shown to be very precise for determination of ^{99m}Tc-DTPA single-sample clearance. The determination was marginally more accurate if the single-sample formula was derived from the entire plasma time-activity curve than from Brøchner-Mortensen's simplified method. The single-sample formula derived for determination of ^{99m}Tc-DTPA clearance (Christensen and Groth) showed slightly, but systematically, higher values when applied on patients investigated with ^{51}Cr-EDTA, than the reference multiple-sample method. Carefulness should, therefore, be observed when deriving a single-plasma sample method from a method that is already simplified. Using the regression coefficients derived for one radiopharmaceutical on another should probably be avoided.

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Gallium-67 Scintigraphy to Predict Response to Therapy in Active Lupus Nephritis

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Gallium-67-citrate has been used to detect inflammation for decades, and ^{67}Ga uptake usually indicates an active, potentially curable lesion. In this study, we determined the value of ^{67}Ga renal scintigraphy for predicting response to therapy in patients with lupus nephritis. **Methods:** Forty-seven patients with lupus nephritis and abnormal serum creatinine or elevated 24-hr urine protein were enrolled. Delayed 48-hr ^{67}Ga imaging was performed to evaluate ^{67}Ga uptake by the kidneys. Serum creatinine and 24-hr urine protein values were obtained at the beginning of this study and after 1 yr of treatment. Serum creatinine was considered abnormal at levels greater than or equal to 1.4 mg/dl and 24-hr urine protein at levels greater than or equal to 1.0 g/day. When the value of serum creatinine or 24-hr urine protein obtained 1 yr after treatment was in the normal range or was 50% of the initial abnormal value, the patient was considered to have good response to treatment. **Results:** Gallium-67 renal scan showed good correlation with the response to therapy in patients with lupus nephritis. In the negative ^{67}Ga scan group, no significant changes in laboratory data were noted between onset of this study and after 1 yr of therapy. In the positive ^{67}Ga scan group, there were significant decreases in serum creatinine and 24-hr urine protein levels 1 yr after treatment, especially in 24-hr urine protein, with p values of 0.019 and 0.0007 respectively, by Student's t-test for dependent samples. Moreover, 11.5% of patients with a negative ^{67}Ga scan had a good response to treatment, whereas 71.4% of patients with a positive ^{67}Ga scan had a good response to treatment. **Conclusion:** We suggest that ^{67}Ga renal scan is a valuable predictor of response to therapy in patients with lupus nephritis.

Key Words: gallium-67 scan; lupus nephritis; serum creatinine; 24-hr urine protein; response to treatment

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The prognosis for patients with lupus nephritis has improved significantly in recent years, partly because of aggressive treatment with immunosuppressive drugs (*1–3*). However,

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