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^{51}Cr-EDTA clearance determined by one plasma sample

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Summary. ^{51}Cr-EDTA clearance was measured in 99 consecutive patients. Based on the individual plasma activity at 180, 200, 220, and 240 min after injection (normalized with respect to injected dose/body surface area), a nomogram and a formula were derived for the relation between clearance and the plasma activity in one sample drawn between 180 and 240 min after injection. The nomogram was tested by the activity in 141 plasma samples from 53 consecutive patients. The clearance values calculated by means of the nomogram were compared to the corresponding clearance value calculated by a conventional standard method. The correlation coefficient for this comparison was $r=0{\cdot}982$.

It is recommended that the nomogram should only be used if clearance values above 30 ml/min are expected.

Introduction

In 1971 Tauxe, Maher & Taylor found it possible to determine the effective renal plasma flow (ERPF) from the activity in only one plasma sample taken at a fixed time after injection of ^{131}I-orthoiodohippurate. They found ERPF to be correlated to the apparent distribution space of the injected tracer. In 1975 Fisher & Veall investigated the relation between the apparent distribution space$_t$ of ^{51}Cr-EDTA at $t=3$, 4, and 5 h after injection, and the glomerular filtration rate (GFR), and advocated that the GFR could be estimated in this way. However, variations between individuals in ECV made absolute estimation of the GFR virtually useless below 30 ml/min. They suggested that correction with respect to body surface area might improve the method. In 1980 Dakubu *et al.* claimed to have achieved this, but the relation between their conclusion and their presentation of data is not clear. In general there is a great desire to simplify and make available methods less invasive. As an extension of the work of Fisher & Veall (1975) we considered it worthwhile to investigate whether a normalization with respect to dose and body surface area could improve the method. Consequently, the purpose of this study was to construct

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a nomogram for the correlation between clearance and corrected plasma activity in one blood sample drawn 3–4 h after injection and to test the range of usefulness of the nomogram in the clinical routine.

Methods

Subjects. 152 consecutive patients referred to the department for routine determination of ^{51}Cr-EDTA clearance.

General procedure. The patients were allowed to move around from the time of the injection of ^{51}Cr-EDTA until blood sampling started. They were not fasting and drinking was not restricted during the investigation.

^{51}Cr-EDTA clearance technique. 1 ml carefully weighed ^{51}Cr-EDTA (V) with an activity of about 100 μCi/ml was given intravenously. A total of 4–5 blood samples were drawn 180–300 min after the injection through an indwelling needle placed in the contralateral forearm. 3 ml plasma from each of the samples was counted for 500 s in a well scintillator to achieve a range of relative standard counting error of 0·5–1·5%.

Determination of the injected dose (Q_O) ^{51}Cr-EDTA (counts/s). A carefully weighed amount of about 0·1 ml drawn from the same batch used for the injection was diluted by a precisely determined factor of approximately 1000 (F) to produce a standard. 3 ml of this standard was counted for 500 s in the scintillator and the activity was expressed in counts ml^{-1} s^{-1} (S). The amount of injected dose Q_O ($Q_O = V \times F \times S$) was in the range of 1–3 · 10^5 counts/s.

The body surface area (A). Was determined according to Du Bois (1927).

Calculations

Standard method. The total clearance (Cl) from the body of ^{51}Cr-EDTA can be determined from

$$Cl = \frac{Q_O}{\int_{t=0}^{\infty} Y(t)\,dt} \qquad (1)$$

where $Y(t)$ is the plasma activity (counts ml^{-1} s^{-1}) at t min after injection (Nosslin, 1965). It is possible to define a final slope from the terminal segment of the plasma activity curve, and according to Bröchner-Mortensen (1972) this can be used to simplify (1) and calculate a preliminary clearance (Cl_1) from

$$Cl_1 = \frac{Q_O}{Y_O/k} \qquad (2)$$

where k (min^{-1}) is the final slope determined by curve fitting (least square method) to the

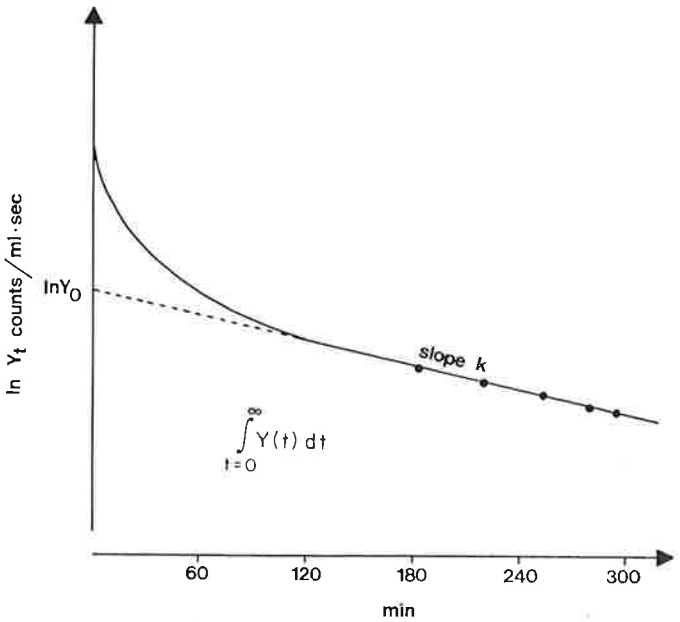

Fig. 1. An example of a plasma activity disappearance curve (Y_t) after single injection of ^{51}Cr-EDTA.

activity of 4–5 plasma samples drawn 180–300 min after injection, and Y_O (counts/ml sec) is the linearily extrapolated intercept on the log ordinate of the final slope (Fig. 1).

It is evident, that Cl_1 overestimates Cl. To make a correction for this an empirically derived relation between these two quantities (Bröchner-Mortensen, 1972) can be used

$$Cl = 0{\cdot}990778\ Cl_1 - 0{\cdot}001218\ Cl_1^2 \qquad (3)$$

The calculation of Cl from the combination of (2) and (3) will in the following be normalized with respect to body surface area by multiplication by $\frac{1{\cdot}73}{A}$ (Smith, 1951) and referred to as the standard method.

The one plasma sample method. According to the fact, that a mono-exponential decrease in plasma activity can be defined after final distribution between the different compartments has been achieved, a close correlation between Cl and ln $Y(t)$ is to be expected, when t exceeds equilibration time. Furthermore, it seems reasonable to assume that $Y(t)$ should be related to the injected Q_O/A. To investigate the correlation between Cl and ln $Y(t)$ we therefore divided $Y(t)$ by Q_O/A before the correlation was tested.

Calculation procedure. All the 152 patients had their clearance measured by the standard method. The study group was formed from the 99 first patients. The composition of this group with respect to age, body surface area, body weight, and clearance is shown in Table 1. Based on the individually calculated Y_O, k, Q_O, and A, a theoretical $Y(t)$ was calculated from $Y(t) = Y_O e^{-kt}$ for t=180, 200, 220, and 240 min after injection and converted to ln $(Y(t) \times A/Q_O \times 10^8)$ m^2/ml.

Table 1. Data of basic study group (49 male and 50 female patients) with respect to age, body area, body weight, predicted body weight calculated from height and age (Natvig, 1956), and clearance

Age (years)	range	19–29	30–39	41–49	50–59	60–82	19–82
	mean	26	34	46	55	68	51
Body surface area (m^2)	range	1·62–2·19	1·44–1·90	1·55–1·93	1·60–2·05	1·26–2·05	1·26–2·19
	mean	1·92	1·69	1·71	1·76	1·70	1·75
Body weight (kg)	range	53–95	36–73	48–76	52–87	38–102	30–102
	mean	69	59	62	66	65	65
Body weight exceeding predicted values more than 20% (No. of patients)		1	0	0	1	8	10
Clearance (ml/min)	range	66–120	50–130	30–104	43–118	14–104	14–130
	mean	89	94	71	75	56	71
Number of patients	total	18	12	16	12	41	99

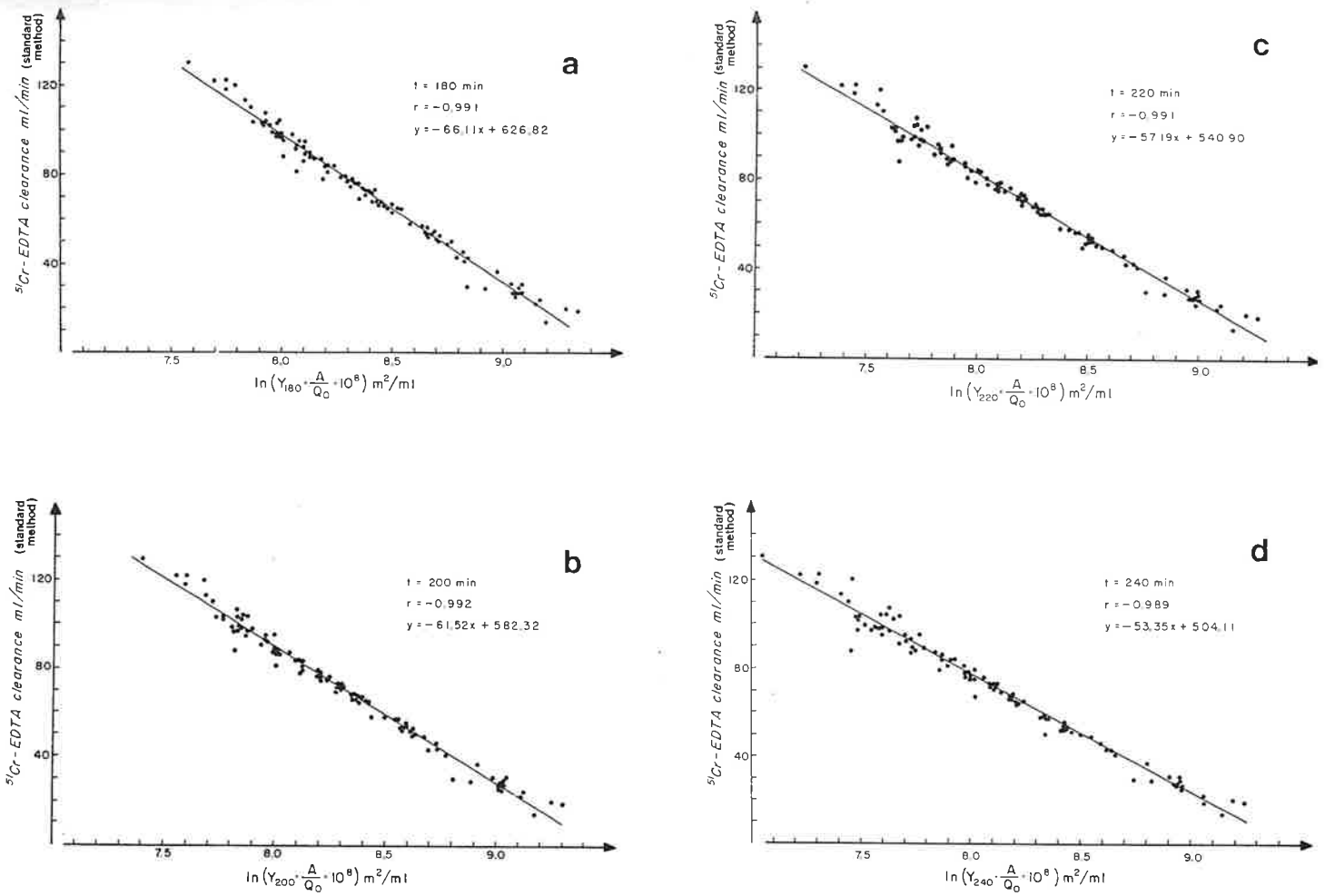

Fig. 2. The relation between clearance and the activity(Y_t) in a single plasma sample normalized to injected dose Q_O and body surface area (A) from 99 patients. Calculated $Y(t)$ values for t=180, 200, 220, and 240 min after injection are shown, and the correlation coefficients and regression lines indicated.

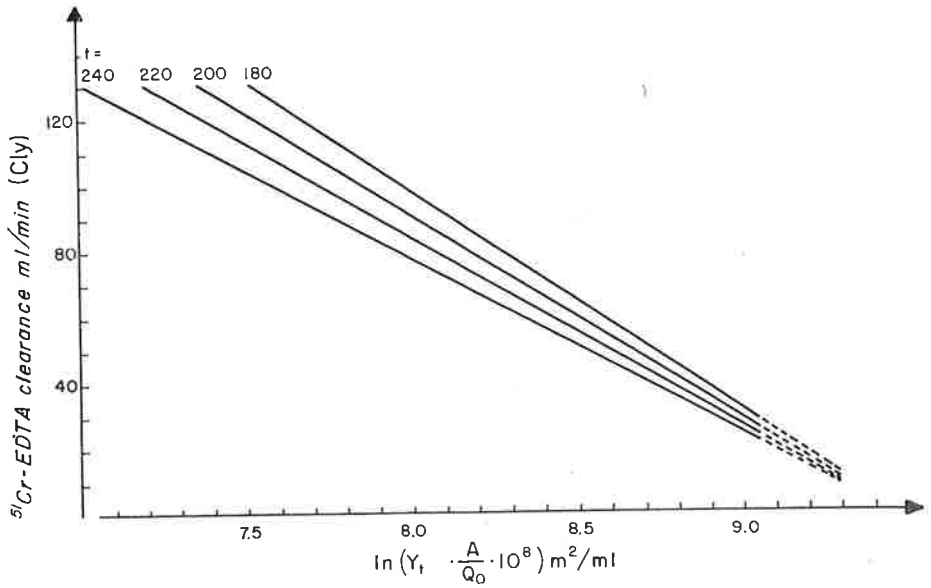

Fig. 3. A nomogram to clearance calculations constructed from the regression lines of Fig. 2. The activity of a single plasma sample, Y_t (counts ml^{-1} s^{-1}) is normalized with respect to injected dose Q_O and body surface area (A) and converted to ln ($Y_t \cdot A/Q_O \cdot 10^8$) m^2/ml. The clearance value is found by linear interpolation between the regression lines of the nomogram.

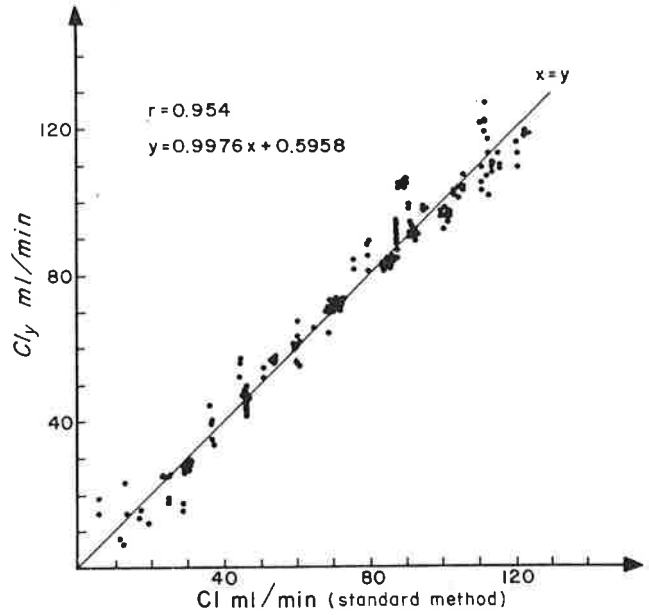

Fig. 4. A comparison of the clearance from 141 blood samples estimated by the standard method (Cl) (see text) and by the nomogram (Cl_y). The regression line is: $Cl_y = 0{\cdot}998\ Cl + 0{\cdot}60$ The correlation coefficient is $r = 0{\cdot}954$. The ratio $\frac{Cl_y}{Cl} \pm$ S.D. is $1{\cdot}00 \pm 0{\cdot}07$ for $Cl \geqq 30$ ml/min.

Results

The correlation between ln $(Y(t)A/Q_O \times 10^8)$ m²/ml for t=180, 200, 220, and 240 min and clearance measured by the standard method is shown in Fig. 2a–d. The correlation coefficients were all better than −0·98. A nomogram (Fig. 3) was then formed from the four regression lines of Fig. 2. The equidistancy of the four lines made it possible to determine clearance (Cl_y) by means of linear interpolation. The correlation coefficient between the slope of the regression lines and the time of their definition (t=180, 200, 220, and 240 min) was r=0·9992. The correlation coefficient between the four intercepts of the regression lines on the ordinate and the time of their definition was, r=−0·9993. This relation between the regression lines was used to derive a formula

$$Cl_y=(0\cdot213t-104)\times\ln\left(Y_t\frac{A}{Q_O}\right)+1\cdot88t-928 \text{ (ml/min per 1·73 m}^2\text{)} \quad (4)$$

for any sampling time between 180 and 240 min after injection.

The nomogram was tested by the results of the last 53 patients of the material. These patients had a total of 141 blood samples drawn between 180 and 240 min after injection. The activity of the samples, $Y(t)$ (counts ml^{-1} s^{-1}), was used directly to calculate ln $(Y(t)\times A/Q_O\times 10^8)$ m²/ml. From each of the 141 ln $(Y(t)\times A/Q_O\times 10^8)$ m²/ml a clearance value Cl_y was found by means of linear interpolation between the regression lines of the nomogram. The Cl_y values are compared to the corresponding Cl values determined by the standard method in Fig. 4. The correlation coefficient was r=0·954. The Cl_y values <25 ml/min were not correlated to Cl (r=0·097).

Cl_y was equally calculated by (4). The correlation coefficient between these 141 Cl_y values and Cl was r=0·982.

Discussion

To construct the nomogram we made the assumption that a final distribution would be achieved 180 min after injection, and that the decrease of plasma activity after final distribution would be mono-exponential, which allowed a final slope to be defined. Bröchner-Mortensen & Rödbro (1976) have shown that when clearance is low, it may last several hours until a final slope can be defined. If clearance is calculated according to (2), the optimal time for blood sampling equals the mean transit time for the tracer in the organism, which in this model is $\bar{t}=1/k$ min (Bröchner-Mortensen & Rödbro, 1976). At this point the area below the activity curve will be least sensitive to an imprecise determination of k. We found the $\bar{t}$ average for the 99 patients of the study group to be 207 min and for the 13 patients of the study group, who had a Cl below 30 ml/min the average $\bar{t}$ was 569 min. This is the most likely explanation to the finding, that the Cl_y values below 25 ml/min were poorly correlated to the corresponding Cl values calculated by the standard method. Considering Fig. 2a & d, there is a tendency, that the distribution around the regression line Y_{180} (Fig. 2a) is larger than around the regression line Y_{240}, (Fig. 2d) with respect to low Cl values, and vice versa with respect to high clearance values. On the other hand, if clearance is 0 ml/min, $Y(t)$ should be expected to be a

constant after final distribution has occurred. Therefore the four regression lines of Fig. 3 should tend to converge at a common intercept on the abscissa, and this is in fact the case.

It was furthermore assumed that there is an inverse relation between $Y(t)$ and body surface area. It has been shown (Novak, 1967) that the extracellular water does not decrease significantly between the ages of 40 and 99 years. Excluding the 13 patients from the study group whose Cl were $\leq$30 ml/min, we did not find any significant difference between the five age groups of Table 1 concerning the relation between ln $(Y_{200} \times A/Q_O \times 10^8)$ m²/ml and Cl. Neither did we find any significant difference between the patients whose weight exceeded predicted values by >20% and the rest of the study group regarding the same relation. Consequently we consider the relation between $Y(t)$ and body surface area to be sufficiently close to fulfill the assumption for Cl>30 ml/min. Yet, if patients are edematous or have severe renal failure this relation is not reliable and we do not recommend the use of the nomogram for values of ln $(Y(t) \times A/Q_O \times 10^8)$ m²/ml $\geq$9·05 m²/ml, or if a clearance $\leq$30 ml/min is suspected. That is, if plasma creatinine exceeds 150 μmol/l for women or 200 μmol for men, (all ages) (Bröchner-Mortensen, Jensen & Rödbro, 1977). From the above it appears that we were not able to extend the range of the usefulness of the method, originally proposed by Fisher & Veall (1975). This opposes the conclusion of Dakubu *et al.* (1980), who investigated the correlation between 107 GFR measurements and the corresponding apparent distribution space$_{t=3h}$ corrected with respect to body surface area. It is not clear on which grounds certain measurements were omitted from their presentation of data (it is only possible to register 91 measurements) and, contrary to their conclusion, the lowest distribution space$_{t=3h}$ was found to represent clearances ranging from 4 to 41 ml/min. We tried to estimate the correlation coefficient, correlating the natural logarithm of the distribution space$_{t=3h}$ to clearance for the 26 subjects in their material, who had a clearance below 30 ml/min. We found r=0·51.

With the limitations mentioned above, the use of the nomogram presented in Fig. 3 may prove useful as a screening method of the GFR or of alterations in the GFR. Routine calculations of the clearance by other methods can easily be double checked for a wide range of values by means of the nomogram. If low clearance values are expected, we recommend the determination of k by multiple blood samples or by monitoring the disappearance rate by external detection (Bojsen, Groth & Rossing, 1981).

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