Measurement of Glomerular Filtration Rate with Technetium-99m DTPA: Comparison of Plasma Clearance Techniques

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We have compared several techniques for measuring [^{99m}Tc]DTPA plasma clearance following single injection to estimate glomerular filtration rate (GFR). Half hourly measurements of disappearance of plasma activity were used to calculate a reference GFR corrected for one-pool assumption and body surface area. Alternative methods involving (i) single blood sample, (ii) two blood samples, (iii) external detector clearance rate, and (iv) a combination of (i) and (iii) were then compared. Closest correlations were obtained with (i) two blood samples at 2 hr and 4 hr (s.e.e. 2.8 ml/min) and (i.v.) external rate constant from 2–5 hr with a blood sample at 3 hr (s.e.e. 3.0 ml/min). Correlations with single blood sample were closest at 3 hr and 4 hr postinjection (s.e.e. 5.4 and 4.5 ml/min, respectively). External detector disappearance rate constant alone was least accurate (s.e.e. >10 ml. min).

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Diethylenetriaminepentaacetic acid labeled with the radionuclide technetium-99m ([^{99m}Tc]DTPA) is used commonly as a radiopharmaceutical for radioisotope renography. It is cleared from the blood stream by the kidneys, and the fractional loss in unit time can be used as a measurement of glomerular filtration rate (GFR). Clearance can be delayed by binding to serum proteins, and for accurate GFR estimation stabilized preparations must be used. In the past, the reference radioisotope method for GFR has used chromium-51 ethylenediaminetetraacetic acid ([^{51}Cr]EDTA), but ^{99m}Tc has the advantage over ^{51}Cr of lower patient radiation dose, less cost, and more suitable gamma emission for scintillation camera use (*1,2*).

We have used a variety of different methods for the estimation of GFR in the same patient using [^{99m}Tc] DTPA, in order to compare the individual accuracy of each method as well as its suitability for routine clinical use in the assessment of adult patients. This first paper compares the results obtained from blood sampling and the use of probe detectors.

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PATIENTS AND METHODS

Prior approval for the study was obtained from the local ethical committee.

Thirty-three renal patients (19–85 yr) undergoing routine radioisotope renography were studied. An accurately measured dose of ~4 mCi (160 MBq) of a stabilized [^{99m}Tc]DTPA preparation* was administered into a left antecubital vein. A plasma sample was taken 1 hr postinjection and again every 30 min for a period of 4 hr, from a cannulated vein on the dorsum of the left hand.

At 1 hr postinjection, and subsequently at 10-min intervals for the following 4 hr, right forearm radioactivity was measured using a specially designed shielded dual scintillation probe counter. An average of two 10-sec counts was recorded.

Also at 1 hr postinjection two small cadmium telluride (CdTe) detectors† were placed on the anterior thorax, either side of the sternum and immediately below the clavicles. Readings from these were recorded at 2-min intervals for a period of 4 hr on a Memolog 500 data storage unit.

ANALYSIS

The plasma kinetics of [^{99m}Tc]DTPA can be described by an open two-compartment mamillary model, in which activity is mixing between vascular and extravascular spaces and being cleared into urine. Once complete mixing has taken place

within the body, these two pools effectively become one and plasma disappearance will reflect GFR (*3*). This is given by the rate constant of exponential clearance (k) for this part of the plasma activity curve. GFR is calculated from the product of this value and the volume of distribution of activity (V_d), thus:

$$GFR = V_d k. \quad (1)$$

The value of V_d is obtained by back extrapolation to zero time to give the estimated activity per unit volume in the volume of distribution (C) had dilution taken place instantaneously.

$$V_d = A/C, \quad (2)$$

where A is the injected activity. The GFR was normalized for body size by correction to a surface area of 1.73 m^2 (*4*).

However, during the period of equilibration a variable quantity of activity is cleared by the kidneys. The resultant reduction in the value for specific activity leads to an overestimation of the volume of distribution (*5*). This error has been assessed experimentally by Brochner-Mortensen (*3*) who derived an empirical correction.

Riggs (*5*) has shown that the one-pool approximation will overestimate the volume of distribution by the following factor

$$\frac{V_d est}{V_d true} = \frac{Z}{(Z - k_u)}, \quad (3)$$

where $Z = (k_u^2 + 4k_e^2)^{1/2}$;

$V_d est$ = Volume of distribution estimated from the one pool approximation;

$V_d true$ = True volume of distribution;

k_u = Glomerular filtration rate as a fraction of plasma volume V_p; and

k_e = Equilibration rate constant between plasma and extravascular space assumed to be equal in both directions.

The one-pool estimates of GFR will then be overestimated by the same factor as the volume of distribution. As shown above, this depends on the values of GFR expressed as a fraction of plasma volume (k_u).

When k_u is low the error is small, but for high GFRs the error is significant. Due to this dependence on k_u which is a measure of the GFR corrected for body size, the GFR is corrected to a body surface area of 1.73 m^2 prior to applying the one-pool approximation correction. This order of performing the two corrections is particularly important in children.

Thus we have used as a reference standard for GFR, for the comparison of alternative methods of measurement, the results obtained from multiple blood sampling between 2 hr and 5 hr, corrected first for body surface area and second for the error arising from a one-pool assumption. The latter adjustment is performed by calculating the surface area corrected one-pool estimate of GFR (GFR_1) and using the equation due to Brochner-Mortensen (*3*) to correct for the errors in the one-pool assumption, i.e.,

$$GFR_{corrected} = 0.990778\ (GFR_1) - 0.001218\ (GFR_1)^2.$$

We have compared several less demanding techniques for measuring plasma clearance to assess their suitability for routine clinical use. The techniques investigated were as follows.

1. The use of two blood samples with identical analysis to the multiple sample clearance above (*6*).

2. The use of one blood sample taken at a fixed time (*7*). It can be shown (Appendix) that provided equilibration between plasma and extravascular space has been achieved,

$$GFR = R_s\ (ke^{-kt_s}), \quad (4)$$

where R_s is the reciprocal fractional activity per unit volume of plasma at time t_s. Since the clearance constant k varies with GFR, then the relationship between R_s and GFR is not exactly linear. However, the term ke^{-kt_s} varies relatively weakly with k (Fig. 1) and the relationship between R_s and GFR is monotonic and approximately linear, thus allowing estimation of the GFR from the activity in a single blood sample. To obtain a surface area corrected GFR, R_s is also corrected for body surface area.

$$R_{sc} = \frac{R_s}{(\text{surface area in } m^2)}.$$

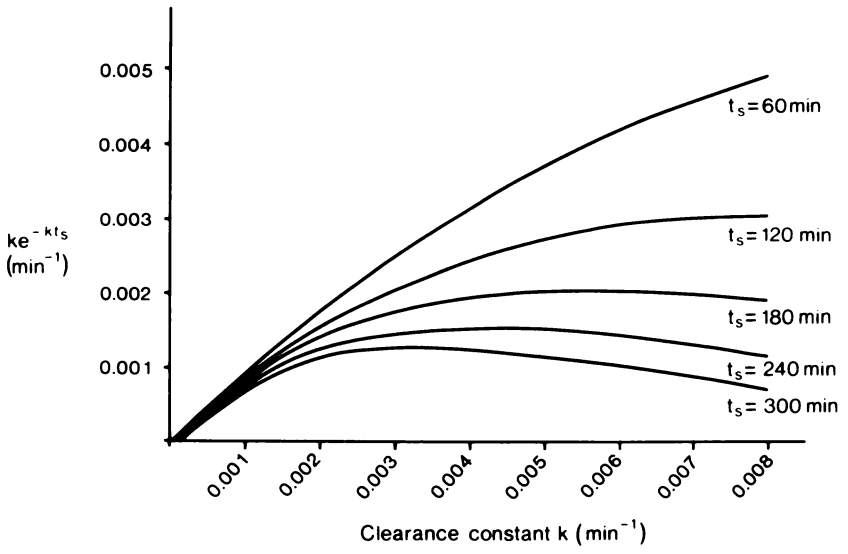

FIGURE 1
Variation of (ke^{-kt_s}) with monoexponential clearance constant k covering the practical range of values of k.

3. Assessment of the disappearance rate constant by external counting (*8*). Since the value of GFR required is that which is normalized to body size then it is reasonable to estimate it from the rate constant of the monoexponential part of the plasma clearance curve. This expresses GFR as a fraction of the volume of distribution cleared per unit time which would be expected to correlate with a surface area corrected GFR.

4. A combination of one blood sample and the disappearance rate constant derived from an external detector (*9,10*). This allows calculation of GFR in ml/min which must be corrected for surface area and the one-pool approximation. From Eq. (4) (Fig. 1) it is clear that even if the rate constant value assessed using external clearance is not exactly the same as the true plasma clearance figure, then the GFR should still be assessed accurately.

Correlations were obtained between each method and the multiple sample plasma clearance of [^{99m}Tc]DTPA using regression analysis to fit the data to a second order polynomial

$$GFR = a + bx_i + cx_i^2,$$

where x_i represents the various parameters calculated by the different methods. For each method the coefficients a, b, and c were calculated together with the correlation coefficient and the standard error of the estimate using the regression equation. The significance of the differences between the standard errors for the different techniques was calculated using the "F" test.

RESULTS

The detailed results from each analysis are shown in Table 1, with individual correlations against multiple sampling plasma clearance of [^{99m}Tc]DTPA.

TABLE 1
Summary of Results of Correlations Between the Different Methods for Estimating GFR and Multiple-Point Plasma Clearance of [^{99m}Tc]DTPA

Method	Number	Coefficients of regression			Standard error of estimate of GFR (ml/min)	Correlation coefficient
		a	b	c		
Two blood sample analysis (GFR in ml/min^{-1})						
1 hr and 2 hr	31	4.78	0.614	0.003	6.6	0.981
2 hr and 3 hr	33	5.506	0.699	0.003	4.3	0.991
2 hr and 4 hr	33	−1.494	0.913	−0.001	2.8	0.996
Single blood sample analysis (reciprocal percentage activity per liter of plasma surface area^{-1})						
at 1 hr	33	−52.48	1115.9	−920.65	15.8	0.885
at 2 hr	33	−41.05	786.69	−774.05	8.4	0.967
at 3 hr	33	−21.66	470.75	−345.16	5.4	0.986
at 4 hr	33	−9.116	295	−145	4.5	0.990
at 5 hr	29	−2.511	213.15	−92.63	7.3	0.978
Disappearance rate constant k (% min^{-1})						
Plasma (2–5 hr)	33	−2.1	142.4	18.14	10.0	0.953
Sodium iodide (2–5 hr)	33	−2.9	170.3	−17.3	12.3	0.929
Cadmium telluride (2–5 hr)	31	−11.2	201.05	−57.16	11.2	0.940
Rate constant and single blood sample						
k (1–2 hr) blood at 2 hr (sodium iodide)	33	13.01	0.849	0.001	8.1	0.969
k (2–3 hr) blood at 3 hr (sodium iodide)	33	1.461	0.975	0	6.4	0.980
k (2–5 hr) blood at 3 hr (sodium iodide)	33	−1.42	1.125	−0.001	3.0	0.996
k (2–5 hr) blood at 3 hr (cadmium telluride)	31	−3.91	1.14	−0.001	3.2	0.995
k (2–5 hr) blood at 5 hr (sodium iodide)	29	−0.542	1.003	−0.0003	3.7	0.994

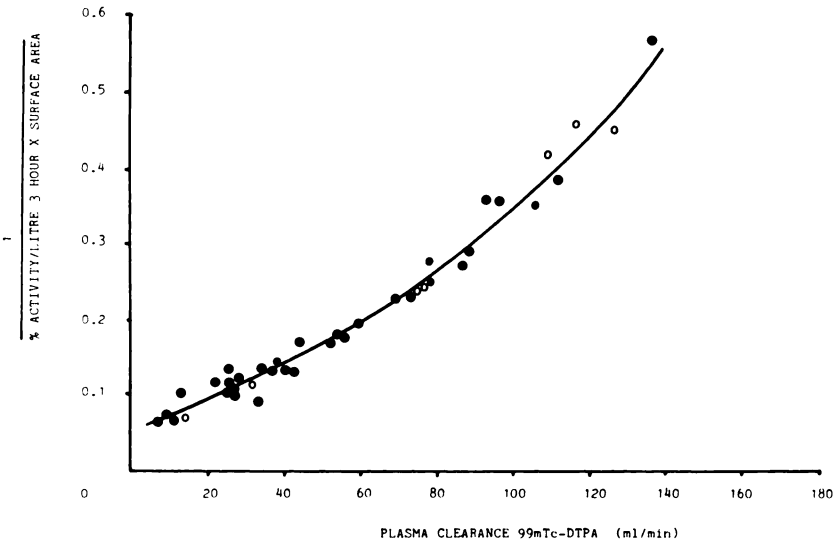

FIGURE 2
Relationship between the percentage activity of a plasma sample taken at 3-hr postinjection and plasma clearance of DTPA. (●): Adult patients in the main study. (○): Results obtained in children.

The best correlation from the analyses carried out was obtained from 2- and 4-hr blood sampling with a standard error of 2.8 ml min^{-1} which was independent of the GFR. This was not significantly different from the result achieved using a single blood sample at 3 hr and the rate constant by external counting obtained by either detection system. Using a single blood sample the correlation with multiple-point plasma clearance was not as good (Fig. 2). Values for GFR in seven children, calculated from a 3-hr sample, are plotted in open circles in Figure 2, using plasma clearance from 2-, 3-, and 4-hr samples as the comparator. The error is similar to that for adults.

DISCUSSION

A variety of techniques have been proposed for the routine assessment of GFR following a single injection of labeled chelate. Measurements can be made of plasma radioactivity, of tissue clearance with probe detectors, or of renal uptake and excretion using a scintillation camera, or a combination of each. We have undertaken direct comparison between these methods so that an optimal routine procedure might be recommended.

In this paper we have presented a comparison of those techniques which use multiple blood sampling and external probe detectors. We have used [^{99m}Tc] DTPA as it is the least expensive and most practical radiopharmaceutical for this purpose. We decided at the outset not to correlate [^{99m}Tc]DTPA clearance with an alternative standard as excellent agreement has been obtained in the past between [^{51}Cr]EDTA and inulin clearance (*2*), and between [^{51}Cr]EDTA and [^{99m}Tc] DTPA clearance (*2*). The use of Pentetate II avoids the problem of protein binding, which can reduce accuracy (*1*) as it contains a stabilizer which limits protein affinity in vitro to < 1%. It was necessary to correct both for body surface area (even in adults), as well as for the overestimation of the distribution volume for the labeled chelate (*3*) in order to compare with methods giving an empirical estimate of GFR.

For routine clinical use, a small measure of accuracy in assessment of GFR may be lost without detriment to patient care. It may therefore be an advantage to employ a technique which reduces patient and laboratory time even though it is not the most accurate technique available.

Using half hourly measurement of clearance of plasma radioactivity as a standard, we obtained correlations using some data common to both sets of measurements. However, the objective was to assess how much data reduction was possible without impairing the accuracy of the estimate to a clinically unacceptable extent.

Using two blood samples, the correlation with multiple-point plasma clearance was excellent, improved results being obtained by using the later blood samples This was probably due to incomplete equilibration at earlier sampling times. In addition, the effect of experimental errors will be reduced by increasing the time between samples. The regression lines are not significantly different from the line of identity so that the values obtained can be taken as absolute GFR provided that the one-pool approximation correction is applied. The commonly used technique of two samples at 2 hr and 4 hr was shown by statistics to give a significantly lower standard error than the others studied. The standard errors obtained were similar to those found by Russell et al. (*11*) who compared the two sample technique with a two-compartment GFR assessment.

The results for a single blood sample show inferior correlation compared with two blood samples taken at around the same time. However, the correlation improves the longer after injection the sample is taken,

reaching an optimum between 3 and 4 hr and then deteriorating significantly at 5 hr. Between 3 and 4 hr after injection corresponds to the minimum variation of the function (ke^{-kt_s}) which is the parameter of proportionality between GFR and reciprocal plasma concentration (Fig. 1). The regression equation for the single sample reciprocal plasma concentration with surface area correction for the adult population has been shown to also apply to children, using a small number of patients. Previous use of the single 3-hr blood sample using [^{51}Cr]EDTA gave a significantly higher standard error of 8 ml/min (*7*). Our results seem comparable with those of Jacobsson (*12*) who used [^{99m}Tc]DTPA with one blood sample and a formula to assess GFR. This study demonstrated standard errors of 6.1 and 5.3 ml/min at 3 and 4 hr, respectively. The current results seem marginally better than those found by Russell et al. (*11*) who used a parameter estimation approach and obtained standard errors of 6.6 and 8.1 ml/min at 3 and 4 hr.

The correlation between disappearance rate constant (k) and GFR was considerably worse than those obtained using blood sample techniques. This rate constant expresses GFR as a fraction of the volume of distribution for DTPA which, corrected for one-pool error and surface area, shows marked variation (median 14.5 l; range 9.7–19.8 l) and explains the relatively poor correlation. Even the k value obtained by blood sampling had a large standard error. The external counting techniques which measure a variable mixture of vascular and extravascular clearance had slightly worse errors. The errors of the two external counters were not significantly different. The correlation coefficient for the arm counter measurement agrees well with the value of 0.92 obtained by McLeod et al. (*8*) who only studied subjects with relatively normal GFR. The correlation for the CdTe detector was slightly better than those previously reported (*13,14*) in subjects with a wide range of renal function.

If a blood sample was used in conjunction with the external counter clearance rate then improved correlation was obtained. As with other results, better correlations were obtained with the later blood samples and the greater the period over which the clearance constant was calculated. Rossing et al. (*10*) demonstrated a correlation of 0.997 between an external rate constant with the CdTe detector up to 160 min combined with a 3-hr blood sample when compared to [^{51}Cr]EDTA plasma clearance. A similar correlation was obtained by Ham et al. (*13*) with a 4-hr rate constant and a 2-hr blood sample. Our results were comparable to these, with marginally worse correlations. The calculation of GFR in this way is relatively insensitive to small errors in clearance constant (Eq. 3).

The relative merits of the above techniques will depend on the clinical application. For the smallest error, the 2- and 4-hr blood samples should be used. Using one blood sample with external counter clearance rate assessment over 5 hr gives similar accuracy but is obviously more time consuming to perform and therefore less suitable for routine clinical use. At the expense of some accuracy a single blood sample alone can also be used and has potential advantages in children. Unfortunately, the less invasive external counter clearance rates without blood sampling do not correlate well enough with GFR to be recommended.

APPENDIX

Assuming equilibration between plasma and extravascular space has taken place, the concentration in plasma is given by

$$P(t) = Ce^{-kt},$$

where C and k are defined as above. Thus, the reciprocal fractional activity per unit volume of plasma at time t_s is

$$R_s = \frac{A}{C} e^{kt_s}.$$

From Eq. (1) the GFR is given by

$$GFR = \frac{Ak}{C}.$$

Thus,

$$GFR = R_s(ke^{-kt_s}).$$

NOTES

* Pentetate II, Amersham International plc, Buckinghamshire UK.

† Type TE101, Pharmacia Electronics, Hillerod, Denmark.

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