Determination of Glomerular Filtration Rate by Single-Plasma Sampling Technique Following Injection of Radioiodinated Diatrizoate

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Measurement of glomerular filtration rate (GFR) based on the radioactivity concentration in a single-plasma sample obtained after the injection of radioiodinated diatrizoate (DTZ) has been described. Simultaneous determinations of GFR by use of DTZ based on multiple-sample plasma disappearance curves and inulin correlate highly. Certain theoretical volumes of distribution (injection dose counts ÷ plasma concentration expressed as counts per liter of plasma) correlate highly with GFR determined by the multiple-sample plasma disappearance curves. For patients with relatively high GFR (>100 ml/min) best correlations were obtained at 120 min; for patients with GFR 60–100 ml/min, best correlations were obtained at sampling times of 150 min after injection and for patients with GFR <60 ml/min, the ideal sampling time was 230 min after injection. For general use the 180-min sampling time may suffice. Since the formulae were found to produce nearly identical GFR values for data obtained from the use of diethylenetriaminepentaacetic acid and DTZ, the former radiopharmaceutical can probably be substituted for diatrizoate using these formulae and sampling times as long as absence of plasma protein binding of the labeled chelate can be demonstrated.

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We (*1*), as well as others (*2*), have reported the advantages of the single-plasma sample technique (*3,4*) for the assessment of effective renal plasma flow (ERPF) over other methods of measurement. This test is based on the use of a regression equation which relates the plasma concentration of injected radioiodine-labeled orthiodohippurate (OIH) at a specific sampling time after injection to ERPF derived by other means.

Attempts to measure glomerular filtration rate (GFR) by similar single-sample techniques following the injection of the chelating agents ethylenediaminetetraacetic acid (EDTA) or diethylenetriaminepentaacetic acid (DTPA) labeled technetium-99m(^{99m}Tc), ytterbium-169 (^{169}Yb), and chromium-51 (^{51}Cr)-DTPA have subsequently been published (*5–7*). The various authors have attested to the superiority of the single-sample technique over other techniques including external body counting (*8*). However, problems with plasma protein binding and impurities present in certain of these radioactive chelators have led us to examine another tracer, radioiodine-labeled diatrizoate (DTZ) where such problems have not been observed. Reported here is the development and evaluation of a single-sample technique using DTZ, including the determination of the optimum plasma sampling time.

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MATERIALS AND METHODS

Selection of Subjects

Ninety-three adult patients with a wide variety of kidney diseases were chosen for study. Ages ranged from 18 to 66 yr in 50 females and from 19 to 57 yr in 43 males. Mean ages were 43 and 46, respectively. Most patients were studied more than once, i.e., before and

after kidney transplant or donation. A total of 134 studies were carried out.

GFR by Inulin Clearances

Simultaneous inulin clearances (C_{in}) were performed by the conventional continuous infusion method on 34 supine patients in the fasting state (*9*). Inulin infusions were made at a rate equal to the excretion rate determined over a 30-min equilibrium period, followed by three 15-min study periods. During each period urine was collected by urethral catheter. Conventional inulin clearance technique was closely patterned after the method of Smith (*10,11*).

GFR by Diatrizoate Clearances (C_{DTZ})

After intravenous injection of 50–100 μCi of iodine-125 (^{125}I) or iodine-131 (^{131}I) DTZ, plasma was harvested from blood sampled in a heparin wetted syringe from another vein through an indwelling needle at ~10-min intervals for the first hour then at 30-min intervals for the remainder of the study. The whole procedure lasted 180 to 240 min. Patients remained sedentary or recumbent over this time interval.

Plasmas and dose standards were counted in a well-type automatic scintillation counter. Radioactivity as cps/ml was plotted on the ordinate of semilogarithmic paper against sampling time (abscissa). Resultant curves were resolved graphically into two exponential lines whose slopes, designated λ_a and λ_b related respectively to the two intercepts A and B (*12*). GFRs were calculated from these elements using the compartment analysis system of Sapirstein (*13*):

$$GFR = \frac{DI \cdot \lambda a \cdot \lambda b}{A.\lambda_b + B.\lambda_a}, \quad (1)$$

where DI represented the total dose injected into the patient in terms of total net cps.

Theoretical volumes of distribution (V_t) or DI/C_t were calculated on each plasma sample throughout the study period. (The word theoretical is used to take into account the fact that DI/C_t does not represent the total intracorporeal volume of distribution since some of the dose has been excreted. It rather indicates that theoretical volume that would contain the tracer at the concentration of the indicator at the sampling site.) C_t represents concentration of radioactivity expressed as cps/l of plasma. These volumes were correlated with GFR calculated from the plasma DTZ disappearance whole curve (Eq. 1 above). GFR was plotted on the ordinate, and the theoretical V_t's were plotted on the abscissa. The plotted data formed a curve whose general formula by least squares fitting was:

$$GFR = G_{max}[1 - e^{-\alpha(V_t - V_{lag})}], \quad (2)$$

where G_{max} represents the theoretical asymptotic maximum value of GFR, e is the base of the natural logarithm, α is the rate constant, and V_{lag} is the intercept of the fitted curve on the abscissa.

The Gauss-Newton iterative method (*14*) was used to produce G_{max}, α, and V_{lag} at the various sampling times.

Occasionally it was necessary to utilize a C_t value at a time when no plasma sampling was obtained. In such cases, interpolated values were obtained from the formula:

$$C_t = Ae^{-2_a t} + Be^{-2_b t}. \quad (3)$$

Standard errors of estimate (Sy.x) were calculated at each sampling time for the entire series and for three separate GFR levels within the series.

The two-compartment model proposed by Sapirstein (Eq. 1) is based on the presumption that the tracer material is injected into a first volume of distribution (V_1), which it leaves by two pathways, one into a second closed volume (V_2) and the other into an open-ended volume (V_3). The flow from V_1 into V_2 (F_{1-2}) is assumed to be equal in magnitude to the flow from V_2 back into V_1 (F_{2-1}). F_{1-2} is a product of the rate constant (k_{1-2}) and V_1. Similarly, F_{2-1} is equal to the product of k_{2-1} and V_2. The flow into V_3, F_{1-3}, is the product of V_1 and k_{1-3} and is unidirectional. F_{1-3} represents GFR. Mean values and standard deviations (s.d.s)for the magnitude of V_1'and V_2, the intercompartmental flows and all rate constants were also calculated.

To determine whether renal handling and body pools of the more extensively used DTPA and DTZ might be similar—thus permitting the use of DTPA data with DTZ formulae—we calculated clearances by both methods from arbitrary volumes of distribution of 10, 20, 40, 60, 80, 100, and 120 l using the formulae based at the appropriate DTZ sampling times and those based on [^{99m}Tc]DTPA presented by Russell (personal communication) derived from Constable et al. (*6*) based on [^{51}Cr]EDTA.

RESULTS

The relationship of GFR by compartment analysis of DTZ calculated from the DTZ plasma disappearance curve to GFR calculated from simultaneously performed conventional inulin clearances was $GFR_{DTZ} = 4.17 + 0.98\ GFR_{in}$ with s.e.e. (Sy.x) of 5.9 ml/min and a correlation coefficient of 0.97. Data are shown in Fig. 1. Since there was a greater number of GFR determinations based on the whole plasma curve than on inulin in the current data base and owing to the high correlation of C_{DTZ} with simultaneously performed inulin clearances, the former was employed as the comparison standard for subsequent calculations.

A general error curve was derived using GFR calcu-

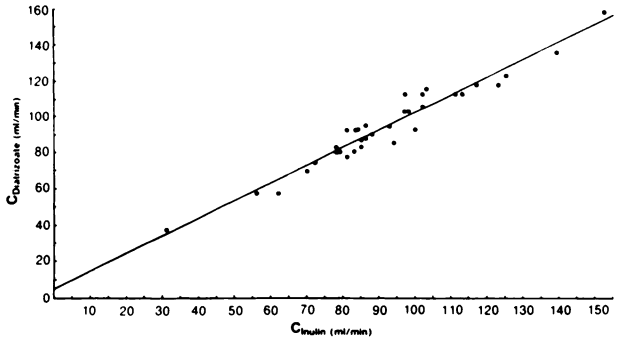

FIGURE 1
Graph of glomerular filtration rate (GFR) derived from simultaneously performed conventional inulin clearances and diatrizoate clearances performed by compartment analysis following single injection of radioiodinated diatrizoate (DTZ). $GFR_{DTZ} = 4.17 + 0.98\ GFR_{in}$; Sy.x = 5.9 ml/min; r = 0.97

lated from the whole DTZ plasma disappearance curve and theoretical volumes of distribution derived at various times. Data are presented in Fig. 2 where Sy.x was calculated and plotted against time after injection. The nadir of the error curve occurred at 180 min after injection and was found to be 7.1 ml/min.

Since it was noted from plots at various sampling times of GFR and V_t that best fits were dependent to some extent on GFR level, individual Sy.x was calculated for GFR > 100 ml/min, 60 to 100 ml/min and < 60 ml/min. These error plots are shown in Fig. 3. Nadirs were observed for patients with the relatively high GFR (>100 ml/min) at 120 min after injection, for those in the middle level (60–100 ml/min) at 150 min and for those with relatively low renal function (<60 ml/min) at 230 min after injection. Respective data plots are shown in Figs. 4, 5, and 6.

Since in practice it is often impossible to obtain blood samples at precise times, calculation of coefficients each minute for 10 min beyond the "ideal" sampling times 120, 150, and 230 min after injection are presented in Table 1.

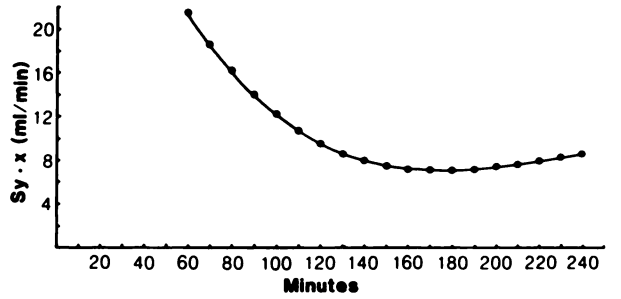

FIGURE 2
Plot of error (standard estimate of error, Sy.x) in ml/min against plasma sampling time in estimation of glomerular filtration rate by single sample technique based on the entire range of GFR values. Least error of 7.1 ml/min was observed at 180 min

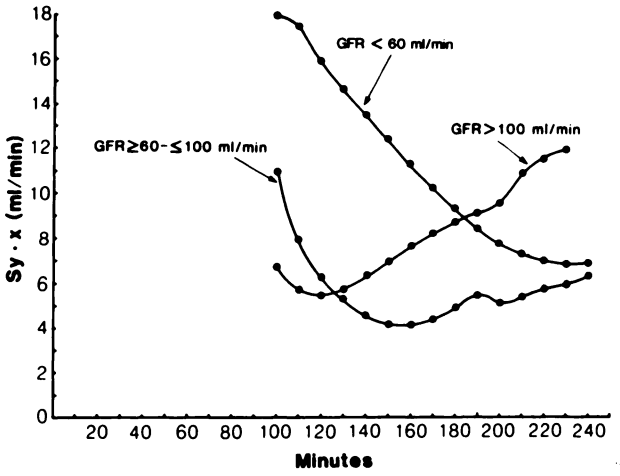

FIGURE 3
Plot of error (Sy.x) of GFR prediction in ml/min against sampling times using single-sample technique based on three different GFR levels. At relatively high GFR (>100 ml/min) optimum sampling time is 120 min (Sy.x 5.5), at GFR 60–100 ml/min optimum time is 150 min (Sy.x 4.2), at GFR >60 ml/min optimum time is 230 min after injection (Sy.x = 6.0)

Means and s.d.s of the theoretical volumes of DTZ, V_1 and V_2, GFR (F_{1-3}), intercompartmental clearances, F_{1-2} and the intercompartmental rate constant k_{1-2}, k_{2-1}, k_{1-3} are all presented in Table 2. Figure 7 shows GFR calculated from arbitrary volumes of distribution by the appropriate formula presented in this paper and GFR calculated from formulae based on DTPA. The correlation coefficient is 0.99.

DISCUSSION

Our data suggest that GFR measurement can be determined noninvasively and easily by a relatively

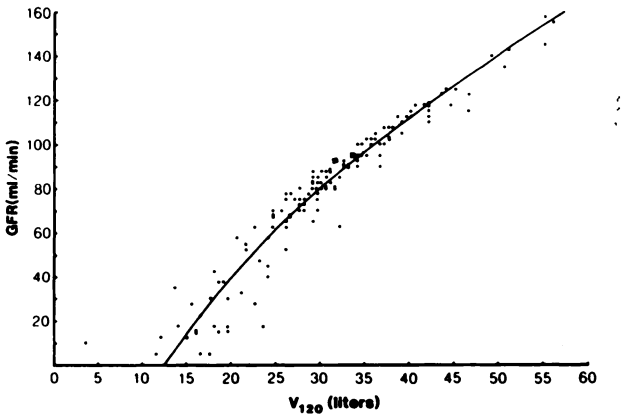

FIGURE 4
Plot of GFR calculated from whole plasma disappearance curves following injection of radiodiatrizoate against plasma concentration reciprocals (theoretical volumes of distribution in liters) obtained at 120 min after injection. Best fit is observed in patients with GFR levels >100 ml/min

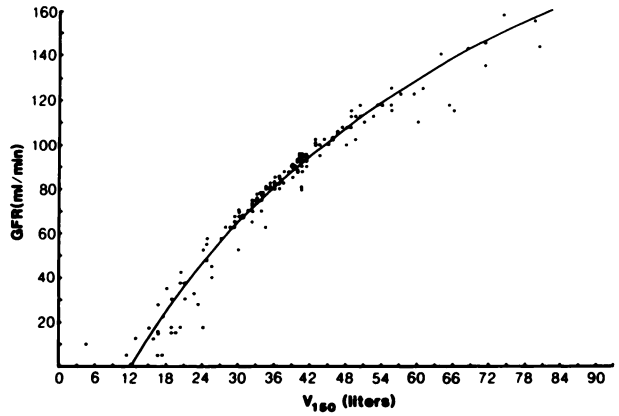

FIGURE 5
Plot of GFR calculated from whole plasma disappearance curves following injection of radiodiatrizoate against plasma concentration reciprocals (theoretical volumes of distribution in liters) obtained at 150 min after injection. Best fit is observed in patients with moderately diminished function, 60–100 ml/min

simple method. The extremely high corrrelation between DTZ clearances and inulin clearances has again been confirmed (*9,12*). The method is quite analogous to that demonstrated for the measurement of ERPF by OIH, but the sampling times are different. The ideal sampling time would appear to vary inversely with GFR level. If a GFR level >100 ml/min were expected, the sampling time of 120 min after injection would be associated with the smallest error using Eq. 2 with coefficients given in Table 1 for this sampling time. Similar coefficients at other sampling times in the table should be used for these patients when clearances are expected to be, respectively, 60–100 ml/min and <60 ml/min. Reasons for this variation in sampling time have been postulated (*15*).

If data of the highest accuracy are desired in a patient whose GFR cannot be estimated prior to testing, it may likely be desirable to obtain plasma samples at all three suggested sampling times. On the other hand, when less rigorous results suffice, as may be frequently obtained in clinical practice, the 180-min sampling time may likely prove to be the most practical overall sampling time. It should be noted, however, that if a patient with extremely poor GFR is studied using the

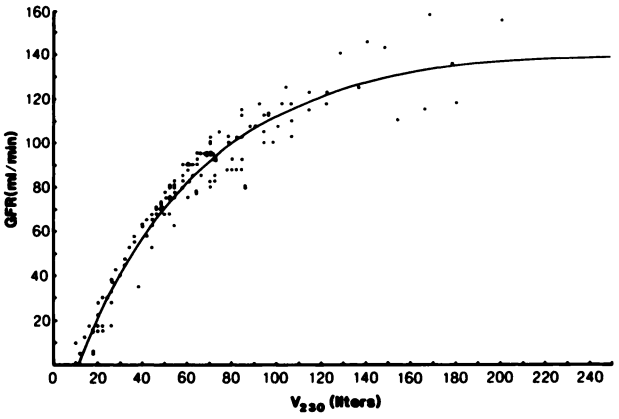

FIGURE 6
Plot of GFR calculated from whole plasma disappearance curves following injection of radiodiatrizoate against plasma concentration reciprocals (theoretical volumes of distribution in liters) obtained at 230 min after injection. Best fit is observed in patients at lower functional level (<60 ml/min)

TABLE 1
Coefficients for GFR Calculation at Various Sampling Times After Injection

Min	G_{max}	α	V_{lag}
	Optimum for GFR >100 ml/min		
120	361.8	0.0124	10.1
121	350.9	0.0127	10.2
122	340.8	0.0131	10.2
123	331.4	0.0134	10.2
124	322.7	0.0137	10.3
125	314.5	0.0140	10.3
126	306.9	0.0143	10.3
127	299.8	0.0146	10.4
128	293.1	0.0149	10.4
129	286.8	0.0152	10.5
130	280.9	0.0155	10.5
	Optimum for GFR 60–100 ml/min		
150	208.8	0.0192	11.0
151	208.8	0.0194	11.1
152	204.5	0.0195	11.1
153	202.5	0.0196	11.1
154	200.5	0.0197	11.1
155	198.6	0.0198	11.2
156	196.8	0.0199	11.2
157	195.0	0.0200	11.2
158	193.4	0.0200	11.2
159	191.7	0.0201	11.2
160	190.1	0.0202	11.2
	Optimum for GFR <60 ml/min		
230	141.7	0.0178	11.0
231	141.4	0.0177	10.9
232	141.1	0.0176	10.9
233	140.8	0.0175	10.9
234	140.6	0.0174	10.9
235	140.3	0.0174	10.8
236	140.0	0.0173	10.8
237	139.7	0.0172	10.8
238	139.5	0.0171	10.8
239	139.2	0.0170	10.7
240	138.9	0.0169	10.7

TABLE 2
Theoretical Volumes of Distribution and Flow Parameters of Diatrizoate

Function	Mean	s.d.
F_{1-2}	222.6 ml/min	99.4 ml/min
V_1	8,510 ml	2,291 ml
V_2	4,458 ml	1,589 ml
k_{1-3}	0.0101	0.0052
k_{1-2}	0.0281	0.0143
k_{2-1}	0.0504	0.0147

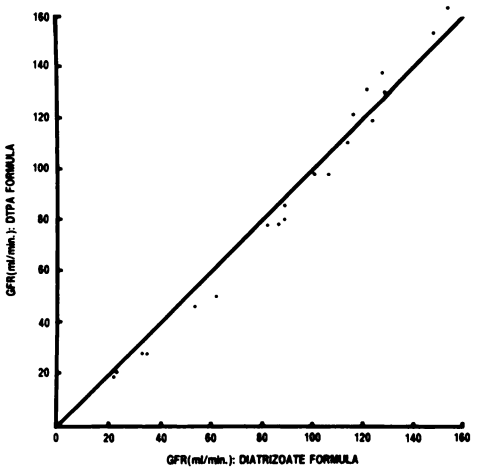

FIGURE 7
Plot of GFR calculated at various arbitrary DTZ concentration reciprocals from 20 to 120 l using optimum DTZ formula (as to sampling time) on ordinate and using the formula based on labeled DTPA at same volume; resultant values are almost identical. Probably, body compartments of two radiopharmaceuticals are quite similar

180-min sampling time, it is probably not possible to distinguish zero from 30 ml/min flow (Fig. 5).

It is probably prudent that patients remain sedentary or recumbent over the time interval between injection and sampling until it can be proved that physical activity has no effect on test results. We have not yet studied this variable.

As with the ERPF studies, the errors do not change very much if the sampling time is slightly different from the "ideal" time. However, it is important that the coefficients appropriate to the actual sampling time be used.

Russell et al. (personal communication) have described a similar single-sample method for the determination of GFR using ^{169}Yb- and ^{99m}Tc-labeled DTPA using formulae based on Constable's work (*6*). They offered a single plasma sampling time and used a parabola to describe the best fit. Since the utilization of the arbitrarily chosen volumes of distribution in the formulae of Russell et al. and those reported here resulted in almost identical "GFR" values, this finding would indicate that the intracorporeal volumes of distribution and renal handling of DTPA (^{99m}Tc or ^{169}Yb) and DTZ are probably equivalent.

Russell et al. cautioned against the use of [^{99m}Tc]DTPA without determining plasma protein binding characteristics (*7*). We have never observed significant plasma protein binding of DTZ.

Constable et al. (*6*) have also shown that EDTA labeled with ^{51}Cr can be used to measure GFR by a single plasma sampling method. These authors chose a single sampling time (180 min) and described errors of 4.4 ml/min. They also used a parabola for best fit, derived at the 180-min sampling time. The error nadir observed by these authors was similar to that observed in our overall series (180 min).

As we observed in the initial exposition of the single-sample method utilizing OIH for the determination of ERPF (*3*), V_1, V_2, F_{1-2}, F_{2-1}, k_{1-2}, k_{2-1} do not correspond precisely with other known physiological parameters. However, the initial mean theoretical volumes of distribution (V_1) of both DTZ and OIH are statistically similar: 8.6 l ± 2.3 for the former and 8.4 l ± 2.0 for the latter.

Obviously, V_1 comprises the plasma volume (as defined by the first volume of distribution of large molecules, e.g., human serum albumin, iron-59 transferrin), but it also includes a space ~5 l larger and in immediate contiguity. In other words, the limiting membrane for large molecules (endothelial cell walls?) appears to be completely permeable to smaller molecules which are in turn limited by some semipermeable perivascular tunic peripheral to the endothelial cell wall. Since the intracorporeal kinetics of human serum albumin follow the same two-compartment mathematical model as does DTZ and since the total albumin pool ($V_1 + V_2$) (*16*) is not statistically different from the V_1 of smaller molecules, it may be that the same tunic delineates the V_2 of macromolecules and the V_1 of such small molecules as DTZ.

Regardless of the lack of information regarding the true nature and significance of the body compartments and intercompartmental flow rates, the procedure as described provides an accurate, rapid, relatively inexpensive, and easily performed test of GFR that does not require the use of a 24-hr urine collection or a scintillation camera.

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