Measurement of Glomerular Filtration Rate: Single Injection Plasma Clearance Method Without Urine Collection

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Glomerular filtration rate (GFR) can be calculated from the plasma clearance of any of several radiopharmaceuticals that are excreted by glomerular filtration. Simplified methods have been proposed that require only one or two plasma samples in lieu of a more complete clearance curve. We examined the error introduced by this simplification. Forty patients were studied using a dual-isotope technique employing [^{99m}Tc]DTPA and [^{169}Yb]DTPA, obtaining eight plasma samples for each clearance curve at intervals from 10 to 240 min after injection. Data were fit to several empirical or semiempirical formulae and also to a two-compartment computer model that permitted GFR estimation from only one or two data points. The computer model gave good fit, but so did several simpler methods. The error that results from replacing the complete clearance curve by a single 3-hr sample was about 8 ml/min (residual s.d.). By using two samples (at 1 and 3 hr), the error could be reduced to 4 ml/min. Recommended one- and two-sample methods are presented.

J Nucl Med 26:1243–1247, 1985

Glomerular filtration rate (GFR) can be calculated from the rate of clearance of tracer activity from the plasma following a single i.v. injection of a suitable radiopharmaceutical. As long as the radiopharmaceutical is excreted solely by glomerular filtration and is not bound to plasma protein or to any other component of blood or other tissue, the GFR can be calculated simply by dividing the administered dose by the integral of the plasma time-activity curve. Approximate methods have been proposed in which the GFR is estimated from only one or two plasma samples rather than from a multisample time-activity curve. These have all been based on chromium-51 ethylenediaminetetraacetic acid ([^{51}Cr]EDTA), except for the work of Jacobsson, who used technetium-99m diethylenetriaminepentaacetic acid ([^{99m}Tc]DTPA) (*1*). There is a problem with the use of [^{99m}Tc]DTPA for quantitative measurements because of a variable degree of protein binding (*2*). That problem was not addressed by Jacobsson. In the present study, we employ [^{99m}Tc]DTPA, with explicit measurement of and correction for protein binding, and with simultaneous use of ytterbium-169 (^{169}Yb) DTPA as an extra check.

In 1971, Tauxe, Maher, and Taylor introduced a single-sample method for estimating effective renal plasma flow (ERPF) from the plasma clearance of iodine-131 orthoiodohippurate (*3*). Subsequent investigators have taken the same approach to estimate GFR from the plasma clearance of [^{51}Cr]EDTA or similar agents. Early investigators fitted their data to purely empirical curves (*4,5*), while later ones often based their calculations on a one-compartment open linear mathematical model (*1,6–8*). The latter approach augments the experimental data by certain physiologic assumptions. Provided these assumptions are valid, such a model can more accurately represent the biological system, particularly for extrapolation outside the range of available experimental data. Two compartments are known to represent the data better than one compartment, but the implicit two-compartment problem cannot be solved analytically. We have treated

Received Feb. 25, 1985; revision accepted Aug. 2, 1985.

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this problem by digital methods for the case in which only one or two data points are given. The results of the true two-compartment model are compared with previous simpler methods.

Plasma clearance curves were measured for 40 patients by drawing eight blood samples from a heparin lock between 10 to 240 min after simultaneous injection of [^{169}Yb]DTPA and [^{99m}Tc]DTPA. The GFR calculated from all eight samples was regarded as the reference value and compared with results obtained by methods using only one or two samples. The resulting errors of measurement were tabulated for each agent, and the one-sample and two-sample methods that gave the best fit are described in detail.

MATERIALS AND METHODS

Patients were drawn from a population that needed GFR measurement for various clinical problems, including a group with normal renal function and recent spinal cord injuries, so that a wide range of GFR values could be included. Patients with edema, which alters radiotracer distribution (*9*), were excluded from the study.

A butterfly infusion set was placed in a peripheral vein. Five millicuries of [^{99m}Tc]DTPA were injected and the syringe flushed with blood, followed by 50 μCi of [^{169}Yb]DTPA after which the syringe was again flushed. Residual activity in the syringe was less than 2% of the dose. Standards were prepared by dilution from duplicate syringes. Eight blood samples were drawn into standard EDTA-anticoagulated vacuum sample tubes at 10, 20, 30, 45, 60, 120, 180, and 240 min after injection, using a vein other than that used for injection. After centrifugation, duplicate samples of plasma and standard were pipetted, counted, and the results averaged. A week later, after decay of ^{99m}Tc, the samples were recounted for ^{169}Yb. The aqueous standard solution of [^{169}Yb]DTPA was pipetted into counting tubes within 8 hr of preparation, since further delay led to deposition of activity onto the glass walls of the container. Technetium-99m DTPA plasma activity was corrected for protein binding as measured by ultrafiltration (*2*).

DATA PROCESSING

The eight-point GFR was calculated from the integral of the plasma time-activity curve, as described in a previous report (*2*). The one-point and two-point GFR estimates were obtained by fitting the data to the open linear two-compartment model of Sapirstein et al. (*10*). In that model, Compartment 1 was the compartment that included the plasma and from which glomerular filtration occurs, and Compartment 2 represented the less accessible portion of the creatinine space. Compartment 2 was assumed to exchange tracer with Compartment 1 at a rate directly proportional to the amount of tracer in each compartment with proportionality constant α. V_1 represented the volume of Compartment 1 and V_2 the volume of Compartment 2. The one-point method employed fixed values for parameters α, V_1, and V_2, obtaining the GFR estimate for each patient by numerical fit (Newton's method) to the single data point. The fixed parameters α, V_1, and V_2, were chosen to give the best least squares fit for all patients taken together as a group. The two-point GFR was obtained in a similar fashion, using α/V_1 and α/V_2 as fixed parameters, V_1 and GFR as variable parameters, and Newton's method for the two-point, two-parameter curve fit.

RESULTS

The result of using two data points to estimate GFR is shown in Fig. 1. The GFR calculated from two measurements (at 1 and 4 hr) agreed closely with that calculated from all eight points (from 10 min to 4 hr after injection). A one-parameter formula initially proposed by Morgan et al. (*5*) was found to be equally satisfactory (Table 1). The two-parameter formula of Brøchner-Mortensen (*11*) also worked well when the parameters were chosen to fit our [^{169}Yb]DTPA or [^{99m}Tc]DTPA data, though the parameters reported by Brøchner-Mortensen for a different agent, [^{51}Cr]EDTA, did not fit our data.

A single sample drawn at 3 hr furnished a reasonable estimate of GFR that is probably adequate for most clinical uses, though the error was about twice that of two samples (Table 2). The two-compartment model again

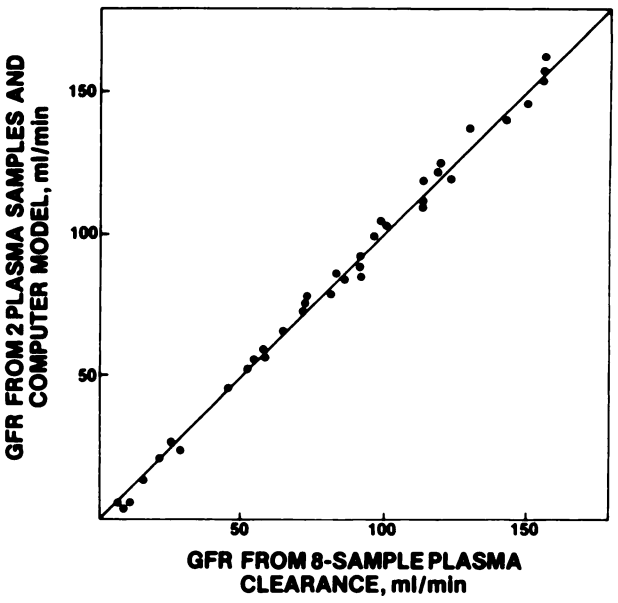

FIGURE 1
GFR estimated from two plasma samples versus reference GFR calculated from eight-point plasma clearance of [^{99m}Tc]DTPA. Estimation from two data points at 1 and 4 hr used digital solution of two-compartment model (Newton's method). Correlation coefficient was 0.998

TABLE 1
Error Introduced by Estimating GFR From Two Plasma Samples Instead of Eight* (ml/min)

Method of calculation	Time of sampling	
	1 and 3 hr	1 and 4 hr
Two-compartment model		
[^{99m}Tc]DTPA	4.4 ± 1.0	3.1 ± 0.7
[^{169}Yb]DTPA	3.2 ± 0.7	2.9 ± 0.6
Morgan Formula (5)		
[^{99m}Tc]DTPA	3.5 ± 0.8	2.6 ± 0.6
[^{169}Yb]DTPA	3.1 ± 0.7	2.7 ± 0.6

*Residual s.d. ± 95% confidence limits, 40 patients, confidence limits from χ^2 distribution with 38 (two-compartment) or 39 (Morgan) degrees of freedom.

gave good results. Comparable accuracy was attained with an equation based on a one-compartment model of the general form used by Senf (*6*), Jacobsson (*1*), and Groth (*7,8*). This equation (Al) is presented in the Appendix. Since it is difficult to adhere to a rigidly predetermined sampling time, we expressed the two parameters of this equation as algebraic functions of time. A sampling time of 3 hr gave the best results, but the time could be as short as 2 hr or as long as 4 hr without much loss of accuracy (Table 2). Tested against our data, alternative one-sample methods (*1,3,7,8,12,13*) gave no better fit than Eq. (A1). Modifying Eq. (A1) to compensate for variations in extracellular volume, as suggested by Groth and Aasted (*8*), also failed to improve the fit.

The two-compartment computer model fit the data quite well (Fig. 1; Tables 1 and 2). The compartmental parameters that gave best fit are listed in Table 3. These parameters were not very sensitive to sampling time, and did not even vary much between [^{99m}Tc]DTPA and [^{169}Yb]DTPA. This model was successful in fitting the data over a wide range of sampling times with few adjustable parameters, but probably has no advantage in clinical use over the simpler methods described in the Appendix.

TABLE 2
Error Introduced by Estimating GFR from Single Plasma Sample Instead of Eight Samples* (ml/min)

Method of calculation	Time of sampling		
	2 hr	3 hr	4 hr
Two-compartment model			
[^{99m}Tc]DTPA	9.3 ± 2.0	6.6 ± 1.4	8.1 ± 1.8
[^{169}Yb]DTPA	12.6 ± 2.8	8.4 ± 1.9	9.5 ± 2.1
Senf Formula (6)			
[^{99m}Tc]DTPA	10.5 ± 2.3	8.1 ± 1.8	9.4 ± 2.1
[^{169}Yb]DTPA	13.7 ± 3.0	10.0 ± 2.2	10.6 ± 2.3

*Residual s.d. ± 95% confidence limits, 40 patients, confidence limits from χ^2 distribution with 37 (two-compartment) or 38 (Senf) degrees of freedom.

TABLE 3
Parameters Giving Best Fit of Two-Compartment Model to Experimental Data (see Data Processing for definition of parameters)

Item	α/V_1, min^{-1}	α/V_2, min^{-1}	V_1, l
[^{99m}Tc]DTPA			
	One-point fit (hr)		
2	0.016	0.026	9.6
3	0.020	0.024	9.5
4	0.019	0.021	8.3
	Two-point fit (hr)		
1 and 3	0.020	0.034	—
1 and 4	0.018	0.035	—
[^{169}Yb]DTPA			
	One-point fit (hr)		
2	0.015	0.029	9.6
3	0.017	0.024	9.3
4	0.016	0.017	7.8
	Two-point fit (hr)		
1 and 3	0.017	0.032	—
1 and 4	0.015	0.032	—

We tried scaling the compartmental volumes for patient size (either by weight or by estimated extracellular fluid volume), and also tried scaling the fluxes (by body surface area). However, scaling for body size failed to improve the fit of the two-compartment model to the adult population studied here.

DISCUSSION

Our estimates of the error involved in estimating plasma clearance of [^{99m}Tc]DTPA or [^{169}Yb]DTPA from a single sample are in general agreement with previous reports using another agent, [^{51}Cr]EDTA. Constable et al. (*12*) claimed an accuracy of 4.4 ml for a single-sample method, but they used only the 3- to 5-hr portion of the time-activity curve for comparison with the single 3-hr sample. Our numbers agree in general with those of other investigators who included both early and delayed measurements in the calculation of GFR from [^{51}Cr]EDTA clearance (*5,13*).

Both [^{99m}Tc]DTPA and [^{169}Yb]DTPA plasma clearances have been shown to approximate GFR, using reference methods other than the classical continuous-infusion inulin clearance (*2*). No agent that is available in the United States for GFR estimation by plasma clearance has been directly tested against the classical method. Iothalamate has been compared with inulin by various groups, but not

by plasma clearance, only by methods based on urine collection (*14,15*). (An agent suitable for methods based on urine collection may not be suitable for plasma clearance methods, since the latter are invalidated by extrarenal excretion or sequestration.) Unfortunately, [^{51}Cr]EDTA for intravenous use is not commercially available in the United States. While direct comparison with classical continuous infusion inulin clearance would be desirable, [^{99m}Tc]DTPA or [^{169}Yb]DTPA agree at least with each other (*2*).

The optimum sampling time for a single sample can be seen from Table 2 to be around 3 hr. We explored the question of optimum sampling time in more detail, replacing the [^{169}Yb]DTPA data for each patient by a fitted two-exponential curve so that the error could be estimated for sample times between those actually used. The minimum error was found to occur at a sample time of 190 min. It has been shown that the optimum sample time for the single-sample method depends on GFR, longer times being required when GFR is low; the same is true of single-sample ERPF measurements (*5,16*). The population we studied, for which 190 min was found optimum, included high, medium, and low GFR patients (Fig. 1). The round number of 3 hr (180 min) is a convenient goal for routine use.

Previously reported two-sample methods have been based on determining the final slope. [There is a known systematic error in the final slope method, for which correction can be made (*5,9,11*).] We relaxed the requirement that both samples be delayed until attainment of the "final slope." Again substituting two-exponential fitted curves for the raw data, we found that the best results were obtained with an initial measurement at 45 to 60 min and the second measurement as late as possible, which was 4 hr in this study. Since prolonged study is inconvenient for routine clinical use, we examined the cost, in terms of accuracy, of reducing the delay for the second sample. We found that the timing of the second sample could be reduced to 3 hr with little loss of accuracy, but that accuracy deteriorated rapidly with further reduction. Sampling at 1 hr and at 3 hr is therefore recommended for routine clinical use.

We were disappointed to find that the two-compartment model, despite being more physiologic, offered little improvement in accuracy over the simpler methods. Evidently, the simpler methods, when applied to an adult population, approach the accuracy that is theoretically attainable. The two-compartment model, when used for two-point GFR estimates, allows for variation of body size and GFR from one patient to another. (Some previous methods correct for variations in GFR (*5,9,11*), though not for body size.) Such correction for body size failed to improve correlation in the adult population studied here, but may prove to be important in pediatric applications.

There has been recent interest in the direct scintigraphic estimation of GFR, using [^{99m}Tc]DTPA. While these methods may have their place in situations where great accuracy is not needed, they have been less accurate in our hands than even a single-sample plasma clearance method (*17*). The total GFR measured from plasma clearance can be divided between the two kidneys, using one of the scintigraphic methods to determine the right/left ratio, for more accurate single-kidney measurements.

CONCLUSION

Simple methods are presented for estimating GFR from one or two blood samples after the injection of either [^{99m}Tc]DTPA or [^{169}Yb]DTPA. The one-sample method is accurate enough for routine clinical use. It does not require that the sample be drawn at a precisely predetermined time, in contrast to methods previously described.

The two-sample method, requiring 3 hr, is nearly as accurate as previous methods requiring 5 hr, and is recommended for investigational use or whenever special accuracy is required. Two samples give results so closely approximating those of eight samples that the use of more than two samples appears unnecessary.

ACKNOWLEDGMENTS

We are indebted to Dr. Joseph Logic for helpful comments and to Ms. Dorothea Ballard for editorial and preparation assistance. This work was supported by the Birmingham Veterans Administration Medical Center, Birmingham, Alabama, and by the National Cancer Institute, DHEW, Grant #1-RO1-CA27252.

APPENDIX

Recommended methods
(Caution: These methods may not be valid in the presence of edema.)

I. Single-sample method (error 8–10 ml/min): Obtain single [^{99m}Tc]DTPA plasma sample at some time (T) between 120 and 240 min (190 min will give the best accuracy, 180 min is recommended for convenience).

Then:

$$GFR = A \ln(D/P) + B, \quad \text{(A1)}$$

where D = dose, counts/min;
P = plasma activity, counts/min-ml;
T = time between injection and withdrawing of sample (min);
A = $-0.278T + 119.1 + 2{,}405/T$;
B = $2.866T - 1222.9 - 16{,}820/T$;
GFR is in ml/min.
(when T = 180 min, then A = 82.42 and B = −800.5.)

The above values of A and B are for [^{99m}Tc]DTPA. If [^{169}Yb]DTPA is used, then

A = $-0.1537T + 73.0 + 5747/T$
B = $1.553T - 741.3 - 50730/T$.

II. *Two-sample method (error 4 ml/min):* Draw first sample at ~ 60 min after injection (exact time = T_1) and the second sample at ~180 min after injection (exact time = T_2).

Then:

$$GFR = \left[\frac{D \ln (P_1/P_2)}{T_2 - T_1} \exp \left(\frac{T_1 \ln P_2 - T_2 \ln P_1}{T_2 - T_1} \right) \right]^{0.979} \quad \text{(A2)}$$

where D = dose, counts/min;
P_1 = plasma activity at time T_1, counts/min-ml;
P_2 = plasma activity at time T_2, counts/min-ml;
GFR is in ml/min.

(The error can be reduced slightly to about 3 ml/min, by drawing the second sample at 240 min. If this is done, use the exponent 0.984 instead of 0.979.)

The above method is for [^{99m}Tc]DTPA. If [^{169}Yb]DTPA is used, then change the exponent from 0.979 to 0.980 when 1- and 3-hr samples are used; 0.981 when 1- and 4-hr samples are used.

III. *Sample calculations for [^{99m}Tc]DTPA:* A programmable hand calculator can be used to evaluate the above formulae. The following data can be used to test the program.

Single-Sample Method:
For T = 180 min;
D = $7 \cdot 10^8$ counts/min;
P = 9,000 counts/min-ml;
we have GFR = 127.7 ml/min.

Two-Sample Method:
For T_1 = 60 min;
T_2 = 180 min;
P_1 = 26,000 counts/min-ml;
P_2 = 9,000 counts/min-mil;
D = $7 \cdot 10^8$ counts/min;
we have GFR = 126.2 ml/min.

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