Simultaneous Estimation of Glomerular Filtration Rate and Renal Plasma Flow

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Comparing the measurements of both glomerular filtration (GFR) and tubular excretion rates [TER(MAG3)] by multi-sample and single-sample methods has been performed after a single bolus injection of 3.7 MBq ^{51}Cr-EDTA plus 37 MBq ^{99m}Tc-MAG3. **Methods:** We studied 17 healthy volunteers and 28 patients with a wide range of renal function. For each plasma clearance curve, nine plasma samples were drawn at intervals from 10 to 240 min after injection of tracers. When comparing individual values for GFR and TER (MAG3) from the tracer dilution spaces (VD) with those derived from the analysis of the entire plasma disappearance curves of two radiopharmaceuticals, a good linear correlation appears (r = 0.96). **Results:** We found that the nadir-error ($S_{y,x}$) for predicted GFR occurs at 180 min (11.0 ml/min/1.73 m^2), while the nadir-error for predicted TER (MAG3) is reached at 90 min (26.4 ml/min/1.73 m^2). **Conclusion:** In the computation of GFR and TER (MAG3) with a single-sample method, it appears that the mean residence time (t) for each tracer represents the optimum plasma sampling time. Our results suggest that the single injection of ^{51}Cr-EDTA and ^{99m}Tc-MAG3 followed by blood sampling twice permits accurate simultaneous estimation of GFR and TER (MAG3) and, after correction of the latter kinetic parameter, effective renal plasma flow.

Key Words: glomerular filtration rate; tubular excretion rate; effective renal plasma flow, chromium-51-EDTA; technetium-99m-MAG3

J Nucl Med 1995; 36:1701–1706

Technetium-99m-mercaptoacetyltriglycine (^{99m}Tc-MAG3) has properties comparable to [^{131}I]orthoiodohippurate (*1,2*), and although the renal clearance of this radiopharmaceutical is little over half that of ^{131}I-hippurate clearance (*3–5*), ^{99m}Tc-MAG3 clearance correlates well with that of [^{131}I]OIH (*4–9*).

For these reasons, and because of its more suitable energy and better dosimetry (*10*), ^{99m}Tc-MAG3 has been proposed as a substitute for [^{131}I]OIH in plasma clearance measurement of effective renal plasma flow (ERPF) (*2,3,5,6,8,10*). Indeed, ^{99m}Tc-MAG3 clearance, which provides a measurement of the tubular excretion rate (TER) of MAG3 [TER(MAG3)] after its correction by a factor 1.5, closely approximates [^{131}I]OIH clearance (*8*). Furthermore, ^{51}Cr-EDTA, when available in a form suitable for human use, is the most reliable agent for monitoring glomerular filtration rate (GFR) because ^{51}Cr-EDTA renal clearance closely approximates inulin clearance (*11–13*). The biological and physical properties of ^{51}Cr-EDTA and ^{99m}Tc-MAG3 led us to study these radiopharmaceuticals for simultaneous estimation of GFR and TER(MAG3) using multi-sample (*3,5,6,14–18*) and single-sample plasma clearance methods (*16,18–22*) in a population of normal volunteers and patients with various renal disorders.

MATERIALS AND METHODS

Subjects

We studied 17 healthy adult volunteers (mean age of 35.3 yr, range 23–47 yr) and 28 patients (11 men, 7 women; aged 26–67 yr) with various renal diseases whose degree of renal impairment had been tested by estimating creatinine clearance according to the formula of Goult-Cockroft [creatinine clearance (ml/min) = 140-age (yr) × weight (kg)/72 × plasma creatinine concentration (mg/100 ml)]. Values from their estimate were corrected by a factor equal to 0.85 in women. Diagnoses were made based on histological appearance and/or clinical findings. In particular (as reported in Table 1), five patients had various types of chronic glomerulonephritis, including IgA glomerulonephritis (Patients 12–24), minimal lesion glomerulonephritis (Patient 16), membranoproliferative glomerulonephritis (Patient 27), mesangiocapillary glomerulonephritis (Patient 10), while other patients had hypertensive angionephrosclerosis (Patients 1, 5, 7, 11, 13, 14, 19, 26), diabetic nephropathy (Patients 20–23), secondary glomerulonephritis (Patients 2, 3, 4, 22) and nephrocarcinoma (Patient 25). Each subject was given a single intravenous composite injection dose containing about 37 MBq ^{99m}Tc-MAG3 (prepared from a commercial kit formulation) and about 3.7 MBq ^{51}Cr-EDTA. The EDTA had a specific activity of about 37 MBq/mg. Separate standards for ^{99m}Tc-MAG3 and ^{51}Cr-EDTA were prepared by dilution from duplicate syringes. After injecting the dose, nine blood samples were drawn into standard EDTA-anticoagulated vacuum sample tubes at 10, 20, 30, 45, 60, 90, 120, 180 and 240 min. Three milliliters of the plasma obtained from each blood sample and 3 ml of the acqueous standard solutions of ^{99m}Tc-MAG3 and ^{51}Cr-EDTA were pipetted into counting tubes and counted using a multichannel Packard Autogamma Spectrometer. To correct the contributions of scattered photons from ^{51}Cr, the total counts in the ^{99m}Tc channel were corrected for spillover from

Received May 17, 1994; revision accepted Oct. 13, 1994.
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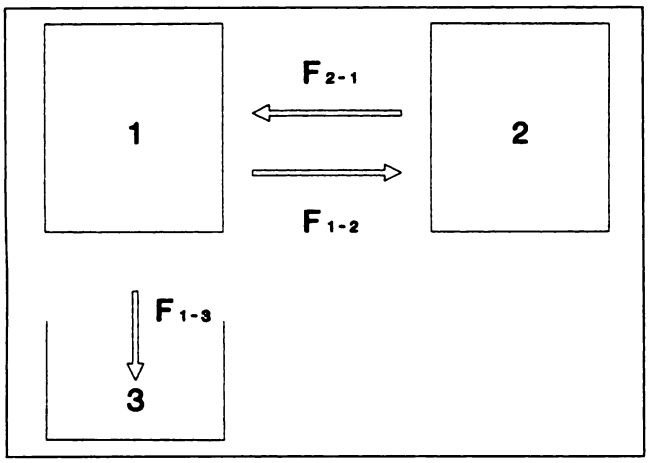

FIGURE 1. Schematic representation of the two-pool model adopted in this study. Compartment 1 (injection compartment) is interconnected with compartment 2 (exchangeable pool). Reservoir 3 represents the kidneys, i.e., the only irreversible loss of the substance from the system.

^{951}Cr. Thereafter, according to the open two-compartment mammillary system (Fig. 1), as suggested by Sapirstein et al. (*23*), ^{51}Cr-EDTA and ^{99m}Tc-MAG3 plasma data were fitted with a sum of two exponential functions of the formula:

$$c(t) = A e^{-\alpha t} + B e^{-\beta t},$$

where c(t) (KBq/ml/1.73 m^2) is the normalized to the body surface of 1.73 m^2 plasma concentration at time t(min), expressed as the percent injected dose (%ID)(MBq)/liter, A and B are the intercepts on the ordinate; and α, β (min^{-1}) represent the slopes of the rapid and slow components. This analysis was performed on a computer using the ENZFITT program (Elsevier/Biosoft, Cambridge, U.K.). According to the Stewart-Hamilton formula, the amount of irreversible removal of tracers from the system versus kidneys (i.e., glomerular filtration rate [or the tubular excretion rate of ^{99m}Tc-MAG3]), were estimated by the equation:

GFR [TER(MAG3)](ml/min/1.73 m^2)

$$= \frac{ID}{\int_0^\infty c(t)dt} = \frac{ID\alpha\beta}{A\beta + B\alpha} = F_{1-3}.$$

The following kinetic parameters were also derived:

- V_1 (liter/1.73 m^2), the volume into which the injection was made (V_1 = ID/(A + B)).
- F_{1-2} (ml/min/1.73 m^2), the intercompartmental flow rate between two compartments of the model adopted (F_{1-2} = $V_1(A\alpha + B\beta)/(A + B) - F_{1-3}$).
- k_{1-2} (min^{-1}), the fractional rate transfer from compartment 1 to compartment 2 ($k_{1-2} = F_{1-2}/V_1$).
- V2 (liter/1.73 m^2), the volume of the interchangeable pool (V_2 = $F_{1-3}\ F_{1-2}/V_1\alpha\beta$).
- V_{tot} (liter/1.73 m^2), the total volume of distribution of tracers ($V_{tot} = V_1 + V_2$).
- $\bar{t}$ (min), the mean residence time of the substance in the system [$\bar{t}$ = (V1 + V2)/F_{1-3}].

Single-Sample Method

We computed the nadir-error ($_{y,x}$) for predicted GFR and TER (MAG3) from the volume of dilution V_D [V_D = ID/c(t)] for either ^{51}Cr-EDTA or ^{99m}Tc-MAG3, as reported by Tauxe et al. (*24*) in each subject. The various values for V_D and the corresponding values for GFR and TER(MAG3) were fitted to an exponential function of the type:

GFR [TER(MAG3)] (ml/min/1.73 m^2)

$$= F_{max}[1 - e^{-\alpha(V_D - V_{lag})}],$$

where F_{max} represents theoretical asymptotic maximum value of GFR [TER(MAG3)], α is the rate constant, and V_{lag} is the intercept of the fitted curve on the abscissa, and to a parabolic function of the type:

GFR [TER(MAG3)] (ml/min/1.73 m^2)

$$= A + B V_D + C V_D^2,$$

where A is the intercept on the ordinate, B the coefficient of the linear term and C the coefficient of the quadratic term. The correlations between V_D and multi-sample GFR and TER(MAG3) were assayed only for values of V_D determined at plasma times around that of the mean residence time ($\bar{t}$) of ^{51}Cr-EDTA and ^{99m}Tc-MAG3 as determined by the multi-sample method.

RESULTS

Multi-Sample Method

For the plasma disappearance curves of injected ^{51}Cr-EDTA and ^{99m}Tc-MAG3, individual values for GFR and TER(MAG3) in normal subjects and in patients are listed in Table 1. The mean value for GFR in normal subjects is 103.8 ± 17.2 ml/min/1.73 m^2 (mean ± s.d.) and 71.8 ± 44.1 ml/min/1.73 m^2 in patients. As reported in Table 2, the mean value for the volume of injection compartment (V_1) for ^{51}Cr-EDTA is 7.59 ± 0.81 liters/1.73 m^2 in normals and 8.35 ± 1.48 liters/1.73 m^2 in patients. The total apparent distribution volume ($V_1 + V_2$) of ^{51}Cr-EDTA in normals is 14.96 ± 3.00 liters/1.73 m^2 and 16.52 ± 3.42 liters/1.73 m^2 in patients. The mean value for the mean residence time for ^{51}Cr-EDTA is 148.0 ± 37.9 min in normals and 300.9 ± 154.1 min in patients with renal disorders. The mean value for TER(MAG3) is 309.5 ± 40.3 ml/min/1.73 m^2 for normals and 223.8 ± 123.1 ml/min/1.73 m^2 for patients. The volume for the injection compartment for ^{99m}Tc-MAG3 is 7.68 ± 4.02 liters/1.73 m^2 for normals compared to 10.32 ± 2.58 liters/1.73 m^2 for patients. The ($V_1 + V_2$) for ^{99m}Tc-MAG3 is 19.64 ± 5.69 liters/1.73 m^2 for normals and 24.32 ± 11.82 liters/1.73 m^2 for patients. Finally, the mean value for the mean residence time for ^{99m}Tc-MAG3 is 63.4 ± 14.9 min for normals and 132.0 ± 87.4 min for patients.

Single-Sample Method

Correlation between V_D and multi-sample GFR and TER(MAG3) was performed at 120, 180 and 240 min for GFR and at 45, 60, 90 and 120 min for TER(MAG3). As reported in Table 3, the nadir-error ($S_{y,x}$) for predicted GFR equals 11.0 ml/min/1.73 m^2 when dilution space for ^{51}Cr-EDTA is computed at 180 min, while $S_{y,x}$ for pre-

TABLE 1
Clearance Estimation in Subjects and Patients (ml/min/1.73 m^2)

Subjects					Patients				
Subject no.	GFR_M*	GFR_S†	$TER(MAG3)_M$‡	$TER(MAG3)_S$§	Patient no.	GFR_M*	GFR_S†	$TER(MAG3)_M$‡	$TER(MAG3)_S$§
1	91.5	85.6	276.2	292.5	1	23.8	13.2	48.4	48.6
2	101.4	93.2	279.1	316.7	2	53.1	46.6	169.6	160.8
3	139.7	158.0	252.1	247.7	3	19.5	14.7	169.0	178.5
4	131.8	77.2	302.7	285.2	4	74.9	75.3	375.3	374.2
5	99.7	109.4	339.2	347.2	5	48.5	48.4	188.6	169.1
6	121.7	120.4	319.8	341.5	6	150.8	147.7	292.7	302.9
7	68.8	79.8	395.6	386.4	7	41.6	44.9	132.1	110.7
8	110.5	99.0	320.7	345.0	8	147.9	147.7	261.7	230.8
9	98.7	92.3	287.9	313.8	9	149.6	144.4	459.5	449.7
10	100.8	100.0	328.2	338.1	10	47.4	45.9	106.8	99.8
11	92.7	87.7	270.9	265.3	11	25.2	32.2	52.6	72.2
12	111.2	104.8	397.3	386.4	12	67.3	72.4	101.4	145.3
13	100.0	96.5	272.7	247.7	13	37.3	30.6	98.8	99.2
14	100.9	101.1	311.7	297.5	14	70.0	70.1	158.6	151.7
15	78.6	83.1	284.2	300.2	15	167.4	159.0	471.6	395.1
16	107.2	102.6	317.8	300.2	16	56.5	57.0	319.0	302.9
17	109.6	105.2	305.7	345.0	17	71.7	74.3	204.5	207.8
mean ± s.d.	103.8 ± 17.2	99.8 ± 18.7	309.5 ± 40.3	315.1 ± 41.8	18	113.8	112.9	175.7	147.5
					19	52.4	53.0	126.1	109.8
					20	41.8	44.6	243.5	271.5
					21	41.9	50.1	143.7	128.4
					22	44.9	70.1	173.8	143.5
					23	45.4	53.6	320.6	290.0
					24	61.1	74.9	379.4	378.3
					25	164.8	161.6	451.0	418.4
					26	66.2	72.8	90.1	168.2
					27	61.8	62.4	275.3	310.9
					28	64.8	70.1	277.1	265.3
					mean ± s.d.	71.8 ± 44.1	73.2 ± 42.6	223.8 ± 123.1	219.0 ± 113.5

GFR_M*= multi-sample GFR; GFR_S†= single-sample GFR (180 min); $TER(MAG3)_M$‡= multi-sample TER(MAG3); $TER(MAG3)_S$§= single-sample TER(MAG3) (90 min).

dicted TER(MAG3) is 26.4 ml/min/1.73 m^2 when dilution space (V_D) for ^{99m}Tc-MAG3 is determined at 90 min postinjection. As reported in Table 1, the mean value for GFR is 99.8 ± 18.7 ml/min/1.73 m^2 in normals and 73.2 ± 42.6 ml/min/1.73 m^2 in the 28 patients with renal diseases, while the mean value for TER(MAG3) is 315.1 ± 41.8 ml/min/1.73 m^2 in normals and 219.0 ± 113.5 ml/min/1.73 m^2 in patients. Wilcoxon analysis of individual value for multi-sample GFR in both study groups indicated no significant difference ($p = 0.72$). No significant differences were found when multi-sample TER(MAG3) values were compared with predicted TER(MAG3) from V_D computed at 90 min ($p = 0.61$). In addition, our results demonstrate (Figs. 2 and 3) a good linear regression between multi-sample and single-sample GFR and between multi-sample and single-sample TER(MAG3) ($r = 0.96$).

DISCUSSION

The mean values and ranges for GFR and TER(MAG3) obtained from the multi-sample method agreed with those reported by other authors (*6,8,14,16–18,22*), suggesting that these kinetic parameters may be suitable reference parameters when evaluating the accuracy of predicted GFR and TER(MAG3) with the single-sample method.

For other kinetic parameters determined by the multi-compartmental approach, we observed that the volume for the injection compartment V_1 for two injected radiopharmaceuticals in normals is approximately two times greater than the plasma volume. According to Tauxe et al. (*24*), this compartment should include, other than plasma, extravascular tissues. Furthermore, the size for the apparent distribution volume for ^{51}Cr-EDTA and ^{99m}Tc-MAG3 (V_2), which in normals equals 7.37 ± 2.49 and 11.96 ± 4.89 liters/1.73 m^2 (*10*), respectively, should be assigned to the tracer being distributed throughout the body but not available to the kidneys for clearance. For ($V_1 + V_2$), of ^{51}Cr-EDTA, there was no significant difference between subjects with low-normal and high normal GFR and normals; for ^{99m}Tc-MAG3, there was a significantly greater difference in between subjects with high-normal TER(MAG3) and normals (37 liters/1.73 m^2 versus 20 liters/1.73 m^2). One could hypothesize that high values for TER(MAG3) resulting in more rapid disposal of ^{99m}Tc-MAG3 molecules from the system as opposed to kidneys imply a decrease in the

TABLE 2
Chromium-51-EDTA and Technetium-99m-MAG3 Kinetic Parameters from Normal Subjects (N) and Patients (P) Using the Two-Compartment Model

Parameter	Subjects	^{51}Cr-EDTA mean ± s.d. (range)	^{99m}Tc-MAG3 mean ± s.d. (range)
F_{1-3} (ml/min/1.73 m^2)	N	103.8 ± 17.2 (60.8 – 139.7)	309.5 ± 40.3 (252.1 – 395.6)
	P	71.8 ± 44.1 (23.8 – 167.4)	223.8 ± 123.1 (48.4 – 471.6)
V_1 (liter/1.73 m^2)	N	7.59 ± 0.81 (5.84 – 9.10)	7.68 ± 4.02 (2.67 – 14.86)
	P	8.35 ± 1.48 (5.60 – 12.06)	10.32 ± 2.58 (4.30 – 14.66)
F_{1-2} (ml/min/1.73 m^2)	N	205.3 ± 85.8 (33.9 – 327.2)	366.4 ± 148.2 (94.5 – 648.7)
	P	186.7 ± 65.9 (79.7 – 370.2)	310.2 ± 191.6 (94.5 – 924.8)
k_{1-2} (min^{-1})	N	0.027 ± 0.013 (0.006 – 0.051)	0.070 ± 0.050 (0.006 – 0.163)
	P	0.023 ± 0.009 (0.008 – 0.048)	0.032 ± 0.024 (0.011 – 0.111)
V_2 (liter/1.73 m^2)	N	7.37 ± 2.49 (3.47 – 14.04)	11.96 ± 4.89 (6.13 – 25.24)
	P	8.17 ± 2.66 (3.40 – 13.60)	14.01 ± 10.91 (4.55 – 47.62)
V_{tot} (liter/1.73 m^2)	N	14.96 ± 3.00 (9.31 – 22.99)	19.64 ± 5.69 (13.93 – 36.53)
	P	16.52 ± 3.42 (9.00 – 23.68)	24.32 ± 11.82 (9.62 – 57.50)
$\bar{t}$ (min)	N	148.0 ± 37.9 (70.6 – 239.3)	63.4 ± 14.9 (45.3 – 91.9)
	P	300.9 ± 154.1 (94.2 – 670.7)	132.0 ± 87.4 (56.9 – 459.0)

mean residence time of tracer in the system and consequently, an expansion of the interchangeable pool V_2. The latter implies an increase in the total volume of distribution. On the other hand, in subjects with low-normal values for TER(MAG3), the average time ^{99m}Tc-MAG3 molecules spend in the system prior to irreversible loss appears significantly higher than in normals ($\bar{t}$: 165 min versus 63 min). Our kinetic studies demonstrate that the fractional transfer rate k_{1-2} (= F_{1-2}/V_1) remains unchanged in subjects with low and high-normal values for GFR because changes in clearance (F_{1-3}) imply variations of both the flow F_{1-2} from compartments 1 to 2 and distribution volume V_1. On the contrary, in subjects with low and high values for TER-(MAG3), significant changes for the fractional transfer rate k_{1-2} occur. These different results may be ascribed to the protein binding of ^{99m}Tc-MAG3, which leads to a reduced value for the fraction of tracer flowing from compartment 1 to 2 (i.e., k_{1-2}). The mean residence time in the 17 normal subjects for ^{51}Cr-EDTA is 148.0 ± 37.9 min and 63.4 ± 14.9 min for ^{99m}Tc-MAG3. In calculating predicted GFR

TABLE 3
Coefficients and Standard Errors ($S_{y,x}$) (ml/min/1.73 m^2) from Dilution Spaces (V_D) (liter/1.73 m^2) at Various Plasma Sample Times (t)

Tracer	t (min)	V_D range	Parabolic A	B	C	$S_{y,x}$	Exponential F_{max}	α	V_{lag}	$S_{y,x}$
^{51}Cr-EDTA										
	120	16–81	−44	4.3	−0.022	15.0	233	0.017	11	15.1
	180	17–108	−36	3.2	−0.013	11.0	215	0.015	13	11.0
	240	20–164	−12	1.9	−0.005	12.0	202	0.010	9	12.0
^{99m}Tc-MAG3										
	45	13–109	−76	9.2	−0.042	31.3	501	0.021	11	30.3
	60	15–132	−36	5.8	−0.017	31.8	614	0.010	9	31.5
	90	17–172	11	3.0	−0.002	26.4	939	0.004	3	26.7
	120	21–233	24	2.0	−0.001	28.8	810	0.003	1	29.3

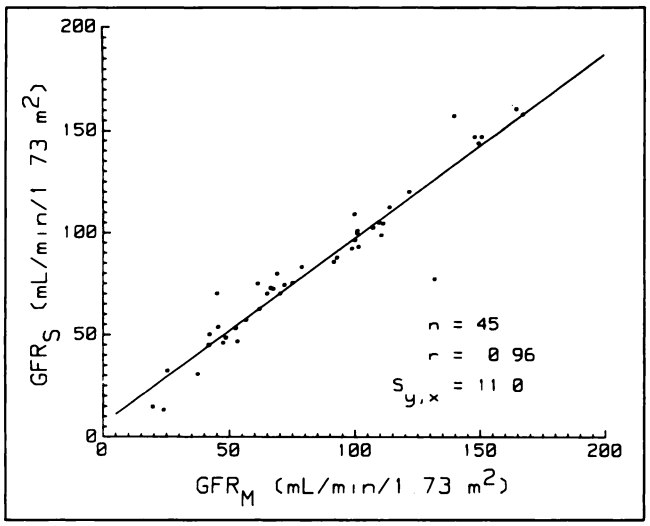

FIGURE 2. Chromium-51 EDTA single-sample clearance values at 180 min (GFR_S (ml/min/1.73 m^2)) correlate well with the reference multi-sample clearance values (GFR_M (ml/min/1.73 m^2). The linear regression equation is y = 6.50 + 0.91.

and TER(MAG3), the optimum plasma time at which to calculate V_D was chosen on the basis of the mean values for $\bar{t}$. Indeed, it was a reasonable assumption that the optimum time for a single sample parallel the residence time characterizing clearance from the system.

Our hypothesis is supported by the data of Tauxe et al. (*24*). These authors studied 116 patients with various renal disorders whose ERPF had been assayed using ^{131}I-OIH and a two-compartment approach. They found a total distribution volume equal to 14 liters and a mean ERPF value equal to 320 ml/min, which implies a ($\bar{t}$) equal to 44 min. This is the same value for the optimum plasma time they observed after performing various time testings. Our values for the nadir-error of GFR from the single-sample method agree with those of several authors. In particular, Fisher et al. (*15*) found a standard error of about 8 ml/min for predicted GFR after ^{51}Cr-EDTA administration when distribution volumes were computed at 180 min. Morgan et al. (*16*) studied 296 patients and observed a nadir-error for predicted GFR after ^{51}Cr-EDTA injection, of about 8 ml/min for 180-min plasma time. In determining GFR by the single-sample method after ^{51}Cr-EDTA injection, Constable et al. (*19*) found an error for predicted GFR from V_D at 180 min plasma time of 4.4 ml/min only. The GFR reference value they used when comparing predicted values with that of plasma ^{51}Cr-EDTA disappearance curves took into account the 3–5 hr portion of this curve.

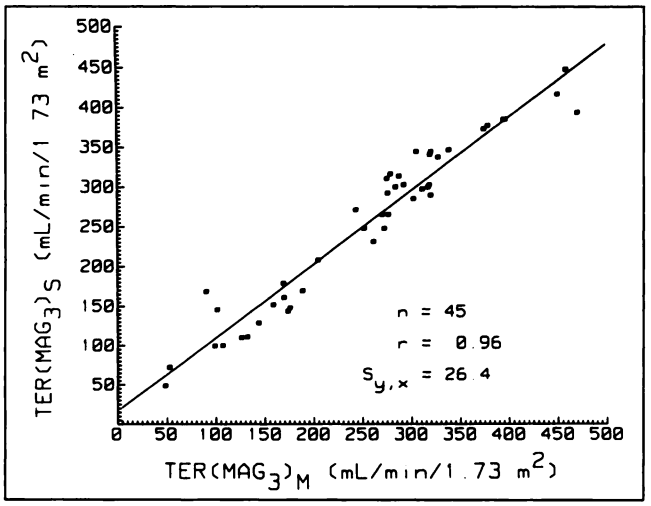

FIGURE 3. Technetium-99m-MAG3 single-sample clearance values at 90 min ($TER(MAG3)_S$ (ml/min/1.73 m^2)) correlate well with the reference multi-sample clearance values ($TER(MAG3)_M$ (ml/min/1.73 m^2)). The linear regression equation is y = 16.49 + 0.93.

For TER(MAG3) determined with the single-sample method, there are discrepancies to other published values. In 35 subjects (including 13 normals) Russell et al. (*18*) observed that the smallest error was present at 45 min postinjection and equalled 19 ml/min. We attribute the discrepancy to the fact that these authors tested the correlation function at 35, 45 and 55 min only, while we tested this correlation at 30, 45, 60, 90 and 120 min. Tauxe et al. (*24*) observed that the nadir-error for predicted ERPF (when [^{131}I]OIH is used) from V_D was reached at 44 min and equaled about 32 ml/min. Since Tauxe et al. (*24*) and Russell et al. (*18*), indicated the same plasma time at 44–45 min for radiopharmaceuticals characterized by different mean residence times, being that the $\bar{t}$ for MAG3 is longer than that for OIH (2), there is reason to think that the nadir-error for ERPF from MAG3 is really reached at plasma times after 45 min. At 45 min, we saw only a "local" nadir-error about 30 ml/min. Our data indicate that a single simultaneous injection of ^{51}Cr-EDTA and ^{99m}Tc-MAG3 followed by two blood samples at 90 and 180 min can result in an accurate estimate of GFR and TER(MAG3) and after correction of the latter parameter, of ERPF. Our technique, apart from being simple, yields a low radiation dose (*10*), which further emphasizes its clinical utility, particularly when filtration fractions are needed.

ACKNOWLEDGMENTS

The authors thank Drs. Giuseppe Villa, Alberto Cifelli and Paolo Calza for their assistance in preparing this manuscript.

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