Estimation of Technetium-99m-MAG_3 Plasma Clearance in Adults from One or Two Blood Samples

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Technetium-99m mercaptoacetyltriglycine (MAG_3) clearance is strongly correlated with effective renal plasma flow and can be used directly as a measure of renal function. For these reasons, formulas were developed for estimation of [^{99m}Tc]MAG_3 clearance based on one or two plasma samples. A two-exponential model provided an excellent fit for 8-point plasma clearance curves obtained from 35 patients having a wide range of renal function. The 8-point [^{99m}Tc]MAG_3 clearance could be estimated from a single point at 43 min with an error of 19 ml/min (residual s.d.) or from two samples at 12 and 94 min with an error of 7 ml/min. The relative errors with MAG_3 are thus comparable to those reported for similar techniques used with [^{131}I]orthoiodohippurate, [^{99m}Tc]diethylenetriaminepentraacetic acid and [^{51}Cr] ethylenediaminetetraacetic acid.

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The clinical value of quantitative renal function measurement is widely recognized. To achieve this simply in a clinical setting, investigators have developed methods to estimate glomerular filtration rate (GFR) or effective renal plasma flow (ERPF) based on either one or two plasma samples following bolus i.v. injection of the appropriate tracer (*1*). As a group, these methods provide a simple clinical procedure for obtaining a reliable estimate of GFR (using technetium-99m diethylenetriaminepentraacetic acid ([^{99m}Tc]DTPA), chromium-51 ethylenediamminotetraacetic acid [^{51}Cr] EDTA), or ytterbium-169 (^{169}Yb) or effective renal plasma flow (ERPF) (using iodine-131 or orthiodohippurate ([^{131}I]OIH) without the necessity of drawing multiple blood samples and applying curve fitting techniques.

Technetium-99m-mercaptoacetyltriglycine (MAG_3, mertiatide) is a new technetium-labeled radiopharmaceutical with properties of renal tubular secretion similar to [^{131}I]OIH demonstrated in both animal and human studies (*2–10*). These findings, coupled with favorable dosimetry of ^{99m}Tc (*9,11*), suggest that [^{99m}Tc]MAG_3 will be widely used and probably replace [^{131}I]OIH and [^{99m}Tc]DTPA in many clinical situations. The clearance of [^{99m}Tc]MAG_3 correlates strongly with OIH clearance (ERPF) and can be used directly as a measure of renal function (*5,7,8,10*). For these reasons, it would be desirable to develop a simple clinical procedure for the estimation of MAG_3 clearance based on a single plasma sample similar to the method Tauxe devised for [^{131}I]OIH (*12,13*). Data from two centers were pooled to develop such a single-sample technique; a two-sample method that provides a slightly better accuracy is also presented.

METHODS

Data were pooled from three previously published studies (*3,8,9*). All studies were approved by the respective Institutional Review Boards and informed consent was obtained from all subjects. Those subjects were included for whom at least eight blood samples were obtained between 9 and 100 min after injection. Thirty-five subjects met these criteria, including 13 normal volunteers and 22 patients with varying degrees of real or suspected renal disease. Two patients had severely impaired renal function and required dialysis. Five of the normal volunteers were studied with an HPLC-purified

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preparation. All other studies were performed with a commercial kit undergoing clinical trials.

The methods of calculation are those used previously for [^{131}I]OIH and [^{99m}Tc]DTPA, and are discussed at length in prior publications (*12–15*). The general approach is described below, together with the results. A simplified account may be found in the appendix.

RESULTS

To obtain a formula for estimating clearance from a single sample, the data were fitted to an equation of the form suggested by Tauxe (*13*) for OIH clearance

$$F = F_{max}\,(1 - \exp(-\alpha\,(1/c\text{-}V_{lag}))), \qquad (1)$$

where F is the clearance and c is the fraction of the administered dose per liter of plasma. The parameters of the equation and the error of fit are shown for various sample times in Table 1. While the error was least at a sampling time of 43 min, the error was not very sensitive to sampling time over the interval 35–55 min, provided the parameters were adjusted to match the sample time. A plot of the clearance calculated from one sample versus that calculated from eight or more samples is shown in Figure 1.

To obtain a formula for estimating clearance from two samples, the data were fitted to an equation previously found useful for estimating [^{131}I]OIH clearance (*15*)

$$F = aF' - b, \qquad (2)$$

where F′ is the clearance calculated by the naive one-compartment model, i.e.

$$F' = \frac{\ln(c_1/c_2)}{t_2 - t_1} \exp \frac{t_1 \ln c_2 - t_2 \ln c_1}{t_2 - t_1}, \qquad (3)$$

where c_1 and c_2 are the plasma activities (fraction dose/ml) at times t_1 and t_2, respectively. The parameters of the equation and the error of fit are shown for various sample times in Table 2. The least error (7 ml/min) occurred when the first sample was drawn at 12 min and the second at 94 min, corresponding to parameter values a = 1.04 (dimensionless), b = 13.7 ml/min. A plot of the clearance calculated from two samples versus that calculated from eight or more samples is shown in Figure 2.

TABLE 1
Parameters of Equation (1) and Residual s.d. σ (ml/min) at Various Sample Times

Time (min)	σ (ml/min)	F_{max} (ml/min)	α (l^{-1})	V_{lag} (l)
35	19.5	677.0	0.0170	7.35
45	18.8	626.9	0.0136	6.15
55	19.3	585.0	0.0115	4.84

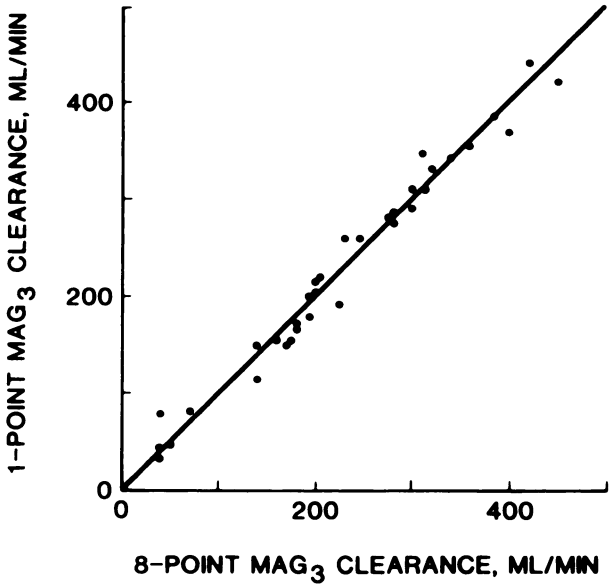

FIGURE 1
Technetium-99m-MAG_3 clearance calculated from single plasma sample at 43 min [Eq. (1)] versus reference clearance calculated from 8 to 11 samples.

The above computations were all performed using two-exponential fits to the observed data. Since fitting, like smoothing or averaging, tends to decrease the effects of measurement error, the errors were recalculated using either one or two points from the raw data. For the 1-point formula, the earliest sample in the interval from 42 to 60 min was used; for the two-point formula, the earliest sample in the interval from 9 to 15 min and the latest sample in the interval from 75 to 100 min were used. The true sample times were used to calculate the parameters of Eq. (1) and Eq. (2) by means of quadratic interpolation in Tables 1 and 2. The root mean square error of the estimates calculated in this way were 20 ml/min for the one-sample method and 8 ml/min for the two-sample method. These values are only slightly higher than those for the fitted curves, despite the fact that the sample timing was not quite optimal and that no use was made of the extra data points.

DISCUSSION

The results presented here are quite similar to those observed previously with [^{99m}Tc]DTPA, [^{131}I]OIH and other agents (*1,14,15*). The errors of measurement are most easily compared when expressed as a percentage of the normal clearance for each agent. Taking 125 ml/min as normal GFR, 600 ml/min as normal ERPF, and 370 ml/min as normal [^{99m}Tc]MAG_3 clearance, the percentage errors for the two-point and one-point methods are 2.1% and 5.5%, respectively, for [^{99m}Tc]

TABLE 2
Parameters a and b of Equation (2) and Residual s.d. (ml/min) in Format a/b (σ) for Various Initial Sample Time t_1 and Final Sample Time t_2

	t_2, min			
t_1, min	70	80	90	100
7.5	1.135/34.3 (13.7)	1.186/32.9 (12.4)	1.229/31.7 (11.4)	1.267/30.6 (11.0)
10	1.041/25.0 (10.3)	1.081/23.5 (8.8)	1.115/22.2 (7.9)	1.144/21.0 (7.7)
12.5	0.957/15.4 (9.0)	0.988/13.9 (7.6)	1.015/12.6 (6.9)	1.037/11.5 (7.0)
15	0.884/6.2 (9.4)	0.909/4.8 (8.3)	0.930/3.5 (7.9)	0.947/2.4 (8.2)

MAG_3, 2.8% and 6.5% for [^{99m}Tc]DTPA (*14*), and 3.3% and 8.0% for [^{131}I]OIH (*15*). The differences between agents are small and of doubtful significance. Of greater significance in clinical applications are the slow clearance of [^{99m}Tc]DTPA that requires prolonging the study to 3 hr, and the high radiation dose and poor imaging qualities of [^{131}I]OIH. In these respects, the advantages of [^{99m}Tc]MAG_3 are apparent.

In most clinical studies to date (*5,8,10,16–21*), there has been strong correlation between [^{99m}Tc]MAG_3 clearance and OIH clearance, showing that [^{99m}Tc]MAG_3 clearance can usually be substituted for OIH clearance as an estimator of ERPF. The ERPF can be estimated by multiplying the MAG_3 clearance by a constant factor that has varied in different hands from 1.4 to 1.8 (*5,8,10,16–21*) and might depend on the source of the drug. (It could also depend on the patient's diagnosis, but the preliminary data do not suggest this). Complete evaluation will require studies in different disease states and ideally should include classic para-aminohippurate (PAH) clearance measurements. Meanwhile, MAG_3 clearance can be used as a functional index (similar to Hilson's perfusion index), as Bubeck suggests (*5*). A report that proteinuria can influence MAG_3 clearance calls for further investigation (*21*). One could speculate that edema would cause less error with [^{99m}Tc]MAG_3 than with the other agents because of its higher protein binding and intravascular retention. The exact relationship between [^{99m}Tc]MAG_3 clearance and true ERPF remains to be determined; studies correlating [^{99m}Tc]MAG_3 clearance with classic continuous-infusion PAH clearance would be highly desirable.

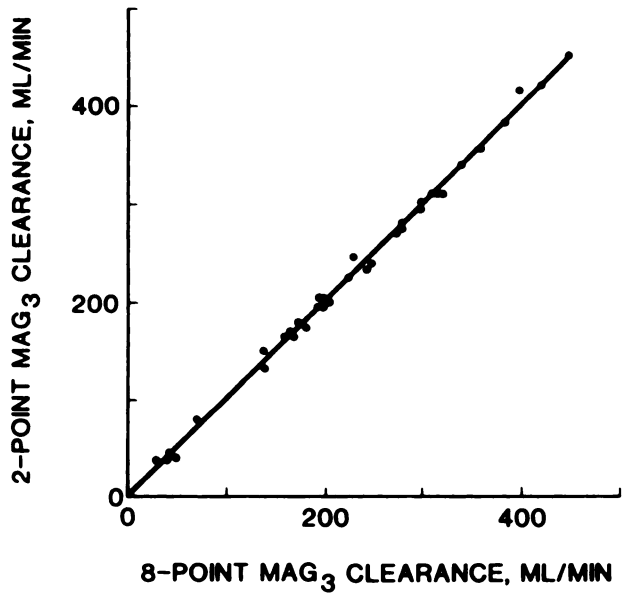

FIGURE 2
Technetium-99m-MAG_3 clearance calculated from two plasma samples at 12 and 94 min [Eq. (2)] versus reference clearance calculated from 8 to 11 samples.

The optimum sample time for single-sample clearance methods depends on the level of renal function, longer sample times being preferred when function is poor, shorter times when function is good (*2,13*). The mathematic optimum of 43 min found in this study refers specifically to a population having a wide range of function (illustrated in Fig. 2) and is a good value to use when function is not known in advance. It can be compared with the value of 44 min found under similar conditions for hippuran (*12,13*). In the two-sample case, the optimum times of 12 and 94 minutes found for [^{99m}Tc]MAG_3 can be compared with the values of 9 and 92 min for hippuran (*15*). The similarities are striking. In contrast, the accurate measurement of [^{99m}Tc]DTPA clearance requires that sampling be delayed for several hours, because of the much slower excretion of [^{99m}Tc]DTPA (*1*).

We have presented both a one-sample method and a more accurate two-sample method. The selection should depend upon the needs of the clinic, but it is our opinion that the single-sample method is sufficient for most clinical uses. Accurate measurement is possible over a fairly wide range of sampling times by using either computer interpolation in Tables 1 and 2 or else the simple hand calculations described in the Appendix.

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APPENDIX: CALCULATIONS FOR SINGLE SAMPLE METHOD

Procedure

Obtain single [^{99m}Tc]MAG_3 plasma sample at some time t between 35 and 55 min.

Then in the absence of edema or ascites

MAG_3 clearance	= $F_{max}(1 - \exp(-\alpha(1/c - V_{lag})))$		
where c	= fraction of dose per liter of plasma, liter^{-1}		
t	= time between injection and withdrawing of sample, min (between 35–55 min)		
F_{max}	= $0.0400\,t^2 - 8.20t + 915$	ml/min	
α	= $6.50 \cdot 10^{-6}t^2 - 8.60 \cdot 10^{-4}t + 3.91 \cdot 10^{-2}$	l^{-1}	
V_{lag}	= $-0.00150t^2 + 0.0100t + 8.79$	l	

The result is in ml/min.

Sample Calculation

If a programmable calculator or computer is used, the following data can be used to test the program.

Given t	= 44 min, dose = $33994 \cdot 10^4$ cts/min, and	
plasma counts	= $11\,558 \cdot 10^3$ cts/min-l	

Then one calculates

c	= $11\,558 \cdot 10^3/33\,994 \cdot 10^4 = 0.0340$	l^{-1}
F_{max}	= 632	ml/min
α	= 0.0138	l^{-1}
V_{lag}	= 6.33	l
MAG_3 clearance	= 172	ml/min

Technical Aspects

Well counters can easily be overloaded by the levels of radioactivity used for imaging techniques. This must be avoided by diluting the sample, decaying it, or using small aliquots. Depending somewhat on the instrument, no more than perhaps 0.3 μCi should be placed in the counter. One way to achieve this is to dilute a duplicate of the dose to 100 ml in a volumetric flask, transfer 1 ml of that to a second 100-ml volume flask, and then count 0.1 ml of both the twice diluted dose and the patient's plasma.

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