Technetium-99m-MAG_3 Clearance as a Parameter of Effective Renal Plasma Flow in Patients with Proteinuria and Lowered Serum Albumin Levels

Roland A. Kengen, Sytse Meijer, H. Beekhuis, and D. Albertus Piers

Departments of Nuclear Medicine and Internal Medicine, University Hospital Groningen, The Netherlands

Although the renal clearance of ^{99m}Tc-MAG_3 is about 60% of the ^{131}I-hippurate clearance, ^{99m}Tc-MAG_3 clearance may be useful to estimate ERPF. In one study, however, proteinuria seemed to influence the MAG_3/hippurate clearance ratio. In order to establish whether proteinuria or serum albumin level has influence on this ratio, a comparison was made between ^{99m}Tc-MAG_3 clearance and ^{131}I-hippurate clearance in 14 patients. There was a good linear correlation between MAG_3 and hippurate clearance, although the standard error of estimate of ERPF from MAG_3 was relatively large, which remained unexplained. No correlation was found between proteinuria and MAG_3/hippurate clearance ratio nor between serum albumin level, GFR, FF, ERPF and the MAG_3/hippurate clearance ratio. We therefore conclude that there is no correlation between proteinuria and albumin level and the MAG_3/hippurate ratio. A reasonable estimation of ERPF with MAG_3 can be made in patients with proteinuria and lowered serum albumin levels although the estimation may be less accurate.

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Since 1985 ^{99m}Tc-labeled mercaptoacetyltriglycine (MAG_3) has been studied intensively as a new renal radiopharmaceutical. Like ^{131}I-hippurate (hippurate), it is rapidly secreted by the renal tubules and a good correlation between the hippurate and MAG_3 clearance has been found (*1–11,13,14*). Despite a lower extraction fraction of MAG_3, it therefore seems possible to use it for determination of the effective renal plasma flow (ERPF). However, in one study (*6*) it was suggested that an increase in proteinuria was the cause of a strongly decreased MAG_3/hippurate clearance ratio (MAG_3/hipp ratio) in one patient who underwent two clearance studies, thereby rendering MAG_3 less reliable as a marker of ERPF. Supporting evidence of that experience has not appeared yet so further study was considered necessary (*4*). In this report, we present data on the clearance of ^{99m}Tc-MAG_3 measured simultaneously with the ^{131}I-hippurate and ^{125}I-thalamate clearances (as representatives of ERPF and GFR (glomerular filtration rate, respectively) in a number of patients with varying degrees of proteinuria.

Because it was not clear from the above-mentioned observation that the increase in proteinuria was in fact the cause of the low MAG_3/hipp ratio, we also correlated serum albumin level, ERPF, GFR, and FF (filtration fraction) with MAG_3/hipp ratio. Finally, we investigated in this group of patients whether the MAG_3 clearance calculated via the IxV/P method (denoted by MAG_3(IxV), IxV = infused activity/min, P = plasma activity/ml), which is not influenced by the inaccuracies of urine collection, gave equal results in comparison to the UxV/P method (denoted by MAG_3(UxV), UxV = excreted activity in urine/min).

PATIENTS AND METHODS

Clearance Studies

Clearance studies of ^{125}I-thalamate, ^{131}I-hippurate, and ^{99m}Tc-MAG_3 were performed simultaneously by the continuous infusion method with urine collection without catheterization. This method is described elsewhere (*12*); it has been used in our hospital as a reliable routine procedure for many years (about 1000 investigations per year); the measured day-to-day coefficient of variation of the hippurate and thalamate clearances were 5% and 2%, respectively (*12*).

In short, after a priming dose of the radiopharmaceuticals (^{99m}Tc-MAG_3: 12 MBq, ^{131}I-hippurate: 0.37 MBq, ^{125}I-thalamate: 0.59 MBq), continuous infusion was started with rates according to estimated renal function (serum creatinine level); after 90 min, when the plasma levels were constant, urine was collected for 4 hr. Renal clearance of hippurate can be accurately calculated via the formula IxV/P (IxV = infused activity/time, P = plasma activity/ml) when the clearance exceeds 100 ml/min, and via UxV/P (UxV = excreted activity in urine/time) when it is less than 100 ml/min (*12*). This same limit was chosen for MAG_3(IxV). The unreliability (overestimation) of the IxV/P hippurate clearance below 100 ml/min was probably due to the relatively large extrarenal clearance of hippurate in this range (*12*).

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For reprints contact: R.A.M. Kengen, Department of Nuclear Medicine, University Hospital Groningen, Oostersingel 59, 9713 EZ Groningen, The Netherlands.

Technetium-99m-MAG_3 was prepared according to the manufacturers instructions (Technescan MAG_3, Mallinckrodt Diagnostics). A 1-ml high concentrated eluate of a ^{99m}Tc-generator (Mallinckrodt Diagnostics) is diluted to a volume of 4 ml with 0.9% NaCl. This volume is added to a vial of Technescan MAG_3, which is subsequently heated for 10 min in boiling water. After cooling down, the preparation is used immediately. Quality control of labeling was performed with thin-layer chromatography. On three occasions, quality control was done with high-performance liquid chromatography according to the manufacturers' instructions. The preparations of ^{125}I-thalamate and ^{131}I-hippurate were suited for measurements of GFR and ERPF (Amersham, ^{131}I-hippurate: <2% free ^{131}I; ^{125}I-thalamate: <0.5% free ^{125}I).

Patients

Twelve patients with proteinuria were studied and two patients without proteinuria were included. Clinical data about these patients are presented in Table 1.

The hippurate and thalamate clearances were performed to estimate ERPF and GFR for clinical reasons; for the addition of ^{99m}Tc-MAG_3, informed consent was obtained. The study was approved by the local medical ethical committee. Nonparametric statistical analysis was performed with the Wilcoxon test for matched pairs and Spearman rank order correlation.

RESULTS

The radiochemical purity of ^{99m}Tc-MAG_3 was always >96%. The patients had varying serum albumin levels, proteinuria, filtration fractions and varying degrees of renal impairment (Table 1). The results of the clearance studies are shown in Table 2. MAG_3(IxV) and MAG_3(UxV) clearance calculations gave good comparable results with a mean difference of 0% ± 4% (1 s.d.). There was a good linear correlation between MAG_3 clearance and hippurate clearance (ERPF) both for MAG_3(UxV) as well as MAG_3(IxV), with s.e.e.s of ERPF from MAG_3 of 55 and 54 ml/min, respectively. The linear regression between MAG_3(UxV) and hippurate clearance is shown in Figure 1.

The mean MAG_3/hipp ratio (Table 2) was 0.53 ± 0.09 for MAG_3(UxV) and 0.53 ± 0.08 for MAG_3(IxV). No significant correlation between the amount of proteinuria or the serum albumin level and this ratio could be estab-

TABLE 1
Patient Data

Patient no.	Diagnosis*	Serum albumin† (g/liter)	Proteinuria (g/24 hr)	ERPF‡ (ml/min)	GFR‡ (ml/min)	FF %
1	MPGN	31	3	170	24	14
2	Amyl.	26	10	195	66	34
3	D. Nefr.	29	13	48	10	21
4	Diff. GN	26	3	625	79	13
5	MGP	31	8	188	30	16
6	MGP	31	7	261	23	9
7	MGP	29	9	113	25	22
8	Nscl.	25	9	315	34	11
9	Vasc.	26	0	486	77	16
10	MGP	27	31	689	45	7
11	D. Nefr.	45	0	182	46	25
12	Foc. GS	22	16	299	20	7
13	Foc. GS	41	7	152	48	32
14	Horsesh. K	49	3	286	95	33

* MPGN = membranoproliferative glomerulonephritis; Amyl. = aa amyloidosis; D. Nefr. = diabetic nephropathy; Diff. GN = diffuse glomerulonephritis; MGP = membraneous glomerulonephritis; Nscl. = nephrosclerosis; Vasc. = vasculitis; Foc. GS = focal glomerulosclerosis; and Horsesh. K = horseshoe kidney.

† Normal range = 34–47 g/liter.

‡ All clearances/1.73 m^2.

TABLE 2
Technetium-MAG_3 Clearances and MAG_3/Hippurate Ratios

Patient no.	MAG_3 (UxV) (ml/min)	MAG_3 (IxV) (ml/min)	MAG_3 (IxV) − (UxV) / MAG_3 (UxV)	MAG_3 (UxV) / Hippurate	MAG_3 (IxV) / Hippurate
1	76	76	0.00	0.45	0.45
2	149	136	−0.09	0.76	0.70
3	26	26	0.00	0.54	0.54
4	342	371	0.08	0.55	0.59
5	106	105	−0.01	0.56	0.56
6	124	123	−0.01	0.48	0.47
7	56	56	0.00	0.50	0.50
8	203	202	0.00	0.64	0.64
9	291	298	0.02	0.60	0.61
10	302	304	0.01	0.44	0.44
11	92	92	0.00	0.51	0.51
12	136	144	0.06	0.45	0.48
13	84	84	0.00	0.55	0.55
14	129	129	0.00	0.45	0.45
Mean			0.00	0.53	0.53
s.d.			0.04	0.09	0.08
			(all clearances/1.73 m^2)		

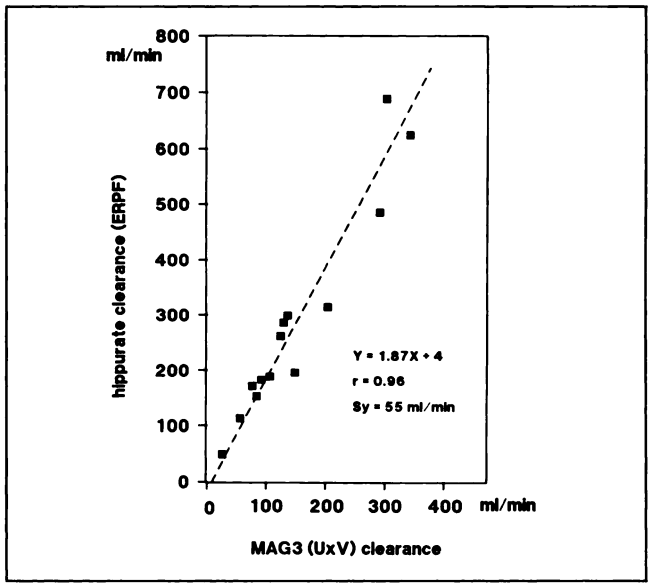

FIGURE 1. Linear regression between MAG_3(UxV) clearance and hippurate clearance. The standard error of estimate of ERPF (hippurate clearance) from MAG_3 clearance is 55 ml/min.

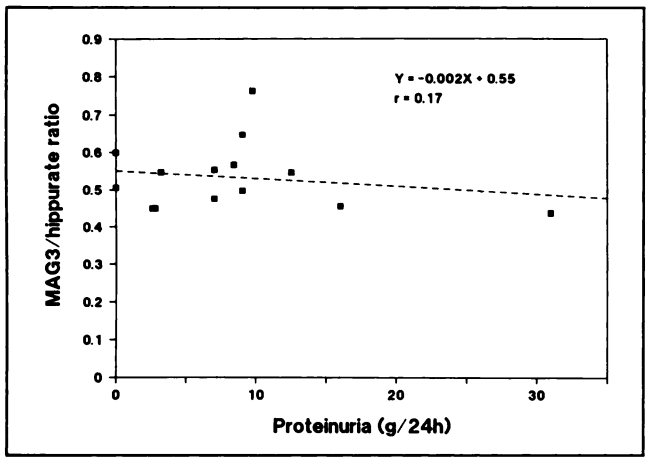

FIGURE 2. No significant correlation between proteinuria and the MAG_3(UxV)/hippurate clearance ratio.

lished (Figs. 2 and 3), nor was there a significant correlation between ERPF, GFR, FF and this ratio (Table 3, only the results for MAG_3(UxV) were shown, the results for MAG_3(IxV) were identical).

DISCUSSION

The equal results of MAG_3(IxV) clearances compared to MAG_3(UxV) clearances can only be explained when MAG_3 is predominantly excreted by the kidneys and extrarenal clearance is low. Earlier experimental proof of this was found in animal experiments in which practically all (99%) of the injected MAG_3 was excreted by the kidneys (*2*).

We could confirm the findings in other studies of a good correlation between MAG_3 and hippurate clearance (*3–11*). The mean clearance ratio in the current study was not different from the mean ratio's in other studies (Table 4). The differences between predicted ERPF and measured ERPF (hippurate clearance) however were relatively high for precise ERPF measurements in this group of patients

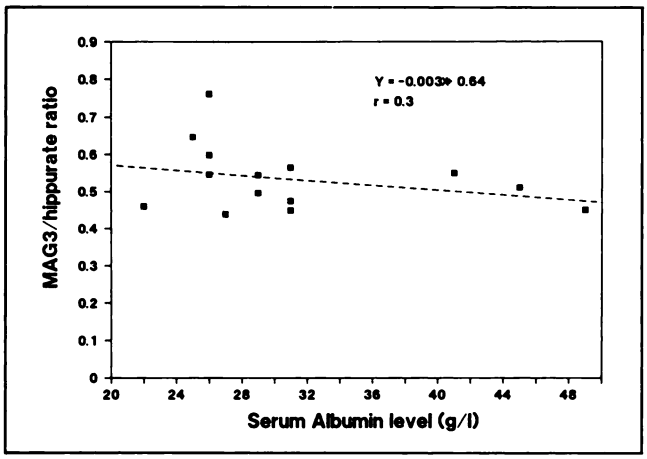

FIGURE 3. No significant correlation between serum albumin level and the MAG_3(UxV)/hippurate clearance ratio.

TABLE 3
Correlation of MAG_3 (UxV)/Hippurate ratio (Y) with Several Parameters (X)

X	Regression equation	r*	p†
ERPF	Y = 0.00X + 0.55	0.14	>0.05
GFR	Y = 0.00X + 0.50	0.22	>0.05
FF	Y = 0.35X + 0.47	0.37	>0.05

* r = Correlation coefficient.
† p = Probability according to Spearman rank correlation.

(Figs. 1 and 4), certainly when the accurate steady state clearance method is taken into account. The reason for this inaccuracy and the deviating MAG_3/hippurate ratio in the patient of Schaap (*6*) is not clear, as we could not find a correlation between several parameters and the MAG_3/hippurate ratio. Perhaps factors other than the quantity of the proteinuria are influential.

In the studies of Schaap (*6*, without the patient with proteinuria) and Bubeck (*7*), which were also done with a steady-state clearance method, the s.e.e.s of ERPF were only 20 and 26 ml/min, respectively. In the studies of Jafri (*5*), Taylor (*9*), and Fraile (*11*), in which MAG_3 clearance was determined with a single-shot method, the s.e.e.s were 70, 57, and 29 ml/min, respectively.

How accurate is MAG_3 clearance in estimating ERPF? PAH is considered to be the gold standard for measurement of ERPF. Hippurate is used because of the elaborate requirements to measure PAH and because it is a good replacement for PAH as a marker of ERPF. We compared the ranges of the MAG_3/hippurate clearance ratios from several recent studies with the ranges of the hippurate/PAH clearance ratios from earlier studies, all with free iodine <2%–3% (Fig. 5). One has to keep in mind that

TABLE 4
MAG_3 Clearance Data from the Literature

Reference	n	MAG_3*	Method†	MAG_3/hipp ± 1 s.d.	X coeff‡
3	88	HPLC	UxV/P	0.67	
	15	HPLC	Ss, Ms		
4	50	Routine	Ss, Ms	?	0.57
8	17	Routine	Ss, Ms	0.61 ± 0.08	
9	15	Routine	Ss, Ms	0.49 ± 0.17	
5	12	Routine	Ss, Ms	0.61 ± 0.08	
6	11	Routine	UxV/P	0.53 ± 0.08	
7	46	HPLC	UxV/P	0.59 ± 0.07	
10	50	?	Ss, Ms	0.62	
11	10	Routine	Ss, Ms	0.61 ± 0.09	
A§	14	Routine	UxV/P	0.53 ± 0.09	

* HPLC = HPLC purificated.
† Ss, Ms = single-shot, multiple-sample and UxV/P = standard method.
‡ X coeff = X coefficient of linear regression.
§ Current study.

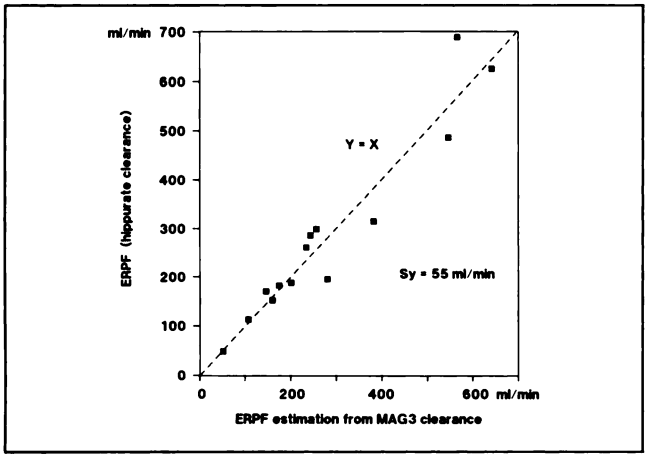

FIGURE 4. Plot of estimated ERPF (from MAG_3 clearance via linear regression) against ERPF (hippurate clearance). The line of identity Y = X is also shown.

such a comparison has only a limited value because a range is far from ideal in comparing studies.

The numbers of patients in the hippurate/PAH studies were larger than in the MAG_3/hippurate studies (mean: 17 versus 11), which enhances the range. The range was chosen, however, because most studies did not mention individual clearance values nor standard deviations of the ratio. Another difficulty in the comparison was the difference in methods: all but one of the PAH studies were done in steady-state conditions with urine collection, while three of the MAG_3 studies were done with a single-injection, multiple-sample method. Additionally, the results of the MAG_3 clearance may be somewhat biased by the fact that PAH and not hippurate is the gold ERPF standard. The data in Figure 5 show that the ranges of MAG_3/hippurate ratios tend to be larger, but that there is also a considerable spread in the hippurate/PAH ratios.

Besides the spread in ratios per study, there is also

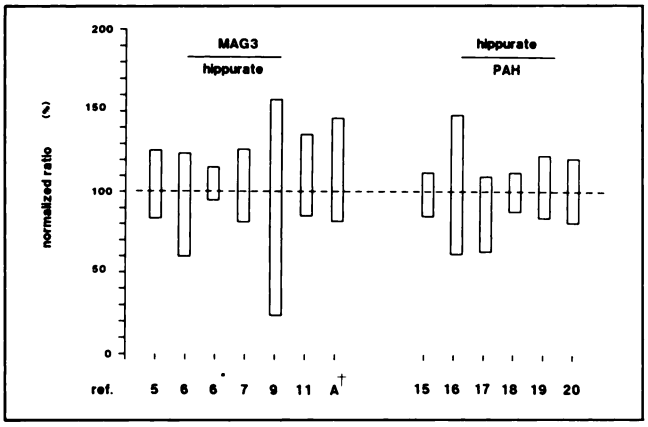

FIGURE 5. Comparison of the range's of the MAG_3/hippurate clearance ratio's (per study) with the range's of the hippurate/PAH clearance ratio's from earlier studies. All mean clearance ratio's were normalized to 100%. Each block indicates the total range per study. Reference 6 and 6*: study of Schaap with and without a patient with proteinuria. A†: current study.

considerable difference in the mean MAG_3/hippurate ratios between the studies (normalized 100% ± 9%, Table 4). But this spread is also present in the mean hippurate/PAH ratios of the studies depicted in Figure 5, which ranged from 0.81 to 0.96 (normalized 100% ± 9%).

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REFERENCES

1. Eshima D, Fritzberg AR, Kasina S, Johnson DL, Taylor Jr A. Comparison of a new Tc-99m renal function agent, Tc-99m-mercaptoacetyltriglycine, with I-131-OIH. *J Nucl Med* 1985;26:5.
2. Fritzberg AR, Kasina S, Eshima D, Johnson DL. Synthesis and biological evaluation of technetium-99m MAG_3 as a hippuran replacement. *J Nucl Med* 1986;27:111–116.
3. Bubeck B, Brandau W, Eisenhut M, Mäurer R, Georgi P. Die Tubuläre Extraktionsrate (TER) von Tc-99m MAG_3: Ein neuer quantitativer Nierenfunktionsparameter. *ZBL RAD* 1987;134:177–178.
4. Russell CD, Thorstad BL, Yester MV, Stutzman M, Dubovsky EV. Quantitation of renal function with technetium-99m-MAG_3. *J Nucl Med* 1988;29:1931–1933.
5. Jafri RA, Britton KE, Nimmon CC, et al. Technetium-99m MAG_3, a comparison with iodine-123- and iodine-131-orthoiodohippurate, in patients with renal disorders. *J Nucl Med* 1988;29:147–158.
6. Schaap GH, Alferink THR, Jong RBJ de, Liem Oe P, Roos JC, Donker AJM. Tc-99m MAG_3: dynamic studies in patients with renal disease. *Eur J Nucl Med* 1988;14:28–31.
7. Bubeck B, Brandau W, Steinbächer M, et al. Technetium-99m labeled renal function and imaging agents. II. Clinical evaluation of ^{99m}Tc-MAG_3 (^{99m}Tc-mercaptoacetylglycylglycylglycine). *Nucl Med Biol* 1988;15:109–118.
8. Müller-Suur R, Bois-Svensson I, Mesko L. A comparative study of renal scintigraphy and clearance with Tc-99m-MAG_3 and ^{123}I-hippurate in patients with renal disorders. *J Nucl Med* 1989;30:2AB.
9. Taylor Jr A, Ziffer JA, Steves A, Eshima D, Delaney VB, Welchel JD. Clinical comparison of I-131-orthoiodohippurate and the kit formulation of Tc-99m-mercaptoacetyltriglycine. *Radiology* 1989;170:721–725.
10. Keske U, Cordes M, Wilfling M, Gahl G, Felix R. Comparison of Tc-99m-MAG_3 and I-131-OIH in patients with normal and impaired renal function. *Clin Nucl Med* 1989;14:P18.
11. Fraile M, Castell J, Buxeda M, Cuartero A, Cantarell C, Domenech Torné FM. Transplant renography: ^{99m}Tc-DTPA versus ^{99m}Tc-MAG_3. A preliminary note. *Eur J Nucl Med* 1989;15:776–779.
12. Donker AJM, Hem GK van der, Sluiter WJ, Beekhuis H. A radioisotope method for simultaneous determination of the glomerular filtration rate and the effective renal plasma flow. *Neth J Med* 1977;20:97–103.
13. Müller-Suur R, Müller-Suur C. Glomerular filtration and tubular secretion of MAG_3 in the rat kidney. *J Nucl Med* 1989;30:1986–1991.
14. Taylor Jr A, Eshima D, Christian PE, Milton W. Evaluation of Tc-99m-mercaptoacetyltriglycine in patients with impaired renal function. *Radiology* 1987;162:365–370.
15. Burbank MK, Newlon Tauxe W, Maher FT, Hunt JC. Evaluation of radioiodinated hippuran for the estimation of renal plasma flow. *Staff Meetings of the Mayo Clinic* 1961;36:372–385.
16. Schwartz FD, Madeloff MS. The use of radiohippuran in the diagnosis of unilateral renal disease. *J Urology* 1962;87:249–257.
17. Schlegel JU, Smith BG, O'Dell RM. Estimation of effective renal plasma flow using ^{131}I-labeled hippuran. *J Appl Physiol* 1962;17:80–82.
18. Wagoner RD, Newlon Tauxe W, Maher FT, Hunt JC. Measurement of effective renal plasma flow with sodium iodohippurate I-131. *JAMA* 1965;187:123–125.
19. Cutler RE, Glatte H. Simultaneous measurement of glomerular filtration rate and effective renal plasma flow with ^{57}Co-cyanocobalamin and ^{125}I-hippuran. *J Lab Clin Med* 1965;65:1041–1049.
20. Skov PE, Hansen HE. Glomerular filtration rate, renal plasma flow and filtration fraction in living donors before and after nephrectomy. *Acta Med Scand* 1974;195:97–103.