Comparison of Iodine-131 OIH and Technetium-99m MAG_3 Renal Imaging in Volunteers

Andrew Taylor, Jr., Dennis Eshima, Alan R. Fritzberg, Paul E. Christian, and Sudhakar Kasina

Department of Nuclear Medicine, University of Utah School of Medicine; and Veterans Administration Medical Center Salt Lake City, Utah

Animal studies have suggested that the nonisomeric N_3S triamide mercaptide ligand, ^{99m}Tc mercaptoacetyltriglycine (MAG_3), may provide a satisfactory ^{99m}Tc-labeled replacement for ^{131}I hippurate (OIH). Sequential 30-min [^{99m}Tc]MAG_3 (5-10 mCi) and [^{131}I]OIH (300 μCi) imaging studies were performed in ten normal volunteers in order to compare the image quality, renal excretion, blood clearance, and time to peak height of the renogram curve. In addition, [^{99m}Tc]MAG_3 (5 mCi) and [^{131}I]OIH (150 μCi) were administered simultaneously in eight volunteers for comparison of 180-min blood and plasma clearances and urine excretion. In the sequential imaging studies, the blood clearance of [^{99m}Tc]MAG_3 was more rapid than [^{131}I]OIH with a mean clearance of 1.30 l/min compared with 0.88 l/min for [^{131}I]OIH ($p < 0.05$). Seventy-three percent of the injected dose of the MAG_3 was excreted by 30 min compared with 66.8% for [^{131}I]OIH. Whole kidney and cortical renogram curves showed no significant difference in the time to peak height for MAG_3 and [^{131}I]OIH. In all subjects, the quality of the [^{99m}Tc]MAG_3 images were clearly superior to [^{131}I]OIH. Following simultaneous injection, blood and plasma clearances for [^{131}I]OIH were more rapid than MAG_3 when determined for multiple time intervals from 0–30 to 0–180 min ($p \leq 0.05$). The 0–30-min clearances of MAG_3 and [^{131}I]OIH were only slightly greater than the 0–180-min clearances and can be used to obtain valid comparisons of the two agents. As in the sequential study, 30-min urine excretion was greater for MAG_3 than [^{131}I]OIH (73.1 compared with 69.6%) but the difference was not statistically significant. Although the differences in the MAG_3 clearances following sequential and simultaneous administration are not satisfactorily explained, the fact that both clearances were rapid, the MAG_3 and OIH renogram curves were quite similar, and 30-min urine excretions of MAG_3 and OIH were essentially identical suggests that MAG_3 may become a ^{99m}Tc replacement for [^{131}I]OIH and further clinical evaluation is warranted.

J Nucl Med 27:795–803, 1986

Radionuclide studies of the kidneys provide a simple noninvasive method of evaluating both total and individual renal function. Commonly used radiopharmaceuticals include iodine-131 (^{131}I) orthoiodohippurate (OIH) and a technetium-99m (^{99m}Tc) agent such as [^{99m}Tc]diethylenetriaminepentaacetic acid (DTPA). Technetium-99m DTPA is cleared by glomerular filtration (*1,2*), has excellent physical properties for imaging and gives a low patient radiation dose per imageable photon (*3*). While these characteristics permit rapid imaging during the first circulation to evaluate renal perfusion, the relatively low renal extraction efficiency of [^{99m}Tc]DTPA and other ^{99m}Tc renal agents may result in a low target to background ratio and nondiagnostic images in patients with impaired renal function. Furthermore, this agent cannot be used to study tubular transport.

Iodine-131 OIH is cleared from the plasma by glomerular filtration (~20%) and tubular secretion (~80%) with a total extraction efficiency by the normal kidney of 70–90% (*3–5*). Unfortunately, [^{131}I]OIH has poor imaging properties, a high radiation dose per imageable photon, and it cannot be used to image renal perfusion. While the high tubular extraction efficiency gives high contrast images that are extremely advantageous for

Received Mar. 5, 1985; revision accepted Feb. 7, 1986.

For reprints contact: Andrew Taylor, Jr., MD, Director of Nuclear Medicine, University of Utah School of Medicine, 50 North Medical Dr., Salt Lake City, UT 84132.

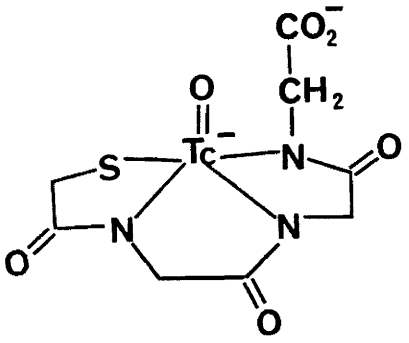
both visual and quantitative interpretation, [^{131}I]OIH gives very poor spatial resolution because the permissible dose that can be injected is limited and its photon energy requires the use of coarse resolution collimators. Iodine-123-labeled OIH (159 keV) is expensive, has a short shelf life ($T_{1/2}$ of 13 hr), and can give a substantial radiation dose to abnormal kidneys due to iodine-124 as a contaminant (*6*). Technetium-99m agents and OIH have distinctly different advantages and disadvantages and the dilemma of choosing between them could be obviated if [^{131}I]OIH could be labeled or replaced with an isotope possessing better imaging characteristics and availability.

In 1979, Davison and co-workers introduced a new class of chelating agents for technetium based on amide nitrogen and thiolate sulfur donor groups (*7*). The initial report stated that a member of the series, ^{99m}Tc*N,N'*-bis(mercaptoacetyl)ethylenediamine ([^{99m}Tc] DADS), demonstrated rapid renal excretion in animals. Further studies in animals and patients confirmed that [^{99m}Tc]DADS was rapidly extracted and cleared by the kidney, but the studies also showed that the biologic properties were still inferior to OIH (*9,10*). The carboxyl derivative ([^{99m}Tc]CO_2DADS) was subsequently synthesized; this agent has two isomers, only one of which showed real potential as an OIH replacement (*11,12*). Since high performance liquid chromatography (HPLC) is required for separation of the two [^{99m}Tc]CO_2 DADS isomers, this agent is unlikely to find wide clinical use. More recently, *p*-aminohippuric acid has been modified by conversion to a carbamoylmethylimmodiacetate (PAHIDA) and labeled with ^{99m}Tc (*13*). The clearance of [^{99m}Tc]PAHIDA in rats was more rapid than a typical GFR agent but it is still <50% that of OIH (*13*).

Continuing efforts have lead to synthesis of an N_3S ligand [^{99m}Tc]mercaptoacetylglycylglycylglycine (MAG_3) which has shown considerable promise in recent animal experiments as a ^{99m}Tc replacement for ^{131}I (*14*). This N_3S ligand has a major advantage over the N_2S_2 derivatives such as [^{99m}Tc]CO_2DADS in that it avoids the problems of stereoisomers. Encouraged by the results of the animal experiments, we further evaluated the potential of this new agent as a ^{99m}Tc substitute for OIH by comparing the renal excretion, blood clearance, image quality, and time to peak height of the renogram curve of [^{99m}Tc]MAG_3 and [^{131}I]OIH in volunteers.

MATERIALS AND METHODS

The proposed structure of [^{99m}Tc]mercaptoacetyltriglycine is illustrated in Fig. 1. The details of its synthesis and characterization will be the subject of a separate report. Briefly, the ^{99m}Tc complex was synthesized by dissolving 1 mg of the benzoate protected ligand in 20 μl of 5 N NaOH. Technetium-99m pertechnetate* in



^{99m}Tc–MAG_3

FIGURE 1
Proposed structure of [^{99m}Tc]MAG_3

saline was added in volumes of 1 to 3 ml depending on the amount of activity needed. One milligram (20 μl of a 50 mg/ml solution) of freshly dissolved sodium dithionite† was added and the mixture was heated at 82°C for 5 min. Finally, ~20 μl of 5 N HCl acid was added to neutralize the reaction mixture. The final preparation was purified by HPLC.

Approval was obtained from our Institutional Review Board to compare [^{131}I]OIH and [^{99m}Tc]MAG_3 in a series of adult male volunteers with no history of renal disease. Following informed consent, a blood sample was obtained from each volunteer for determination of serum creatinine.

Sequential Imaging Studies

Ten sequential imaging studies were performed. Each volunteer was positioned in a supine position and a large field-of-view gamma camera was positioned posteriorly beneath the kidneys. After an i.v. injection of 300 μCi of [^{131}I]OIH, analog images were obtained at 2-min intervals for 30 min using a 360 keV collimator and a 20% window centered over the 364 keV photon peak of ^{131}I. The camera was also interfaced to a computer‡ and digital images were recorded at 20-sec intervals for 30 min. In eight of the ten volunteers, 1-ml blood samples were obtained at 3, 6, 9, 12, 15, 20, 25, and 30 min postinjection and the blood clearance was calculated based on a single injection two-compartment model (*15,16*). Each volunteer was asked to void at 30 min postinjection and the urine was counted to determine the amount excreted. Prevoid and postvoid images were obtained to correct for postvoid residual. As soon as the OIH portion of the study was complete, the volunteer received an i.v. injection of 5–10 mCi of [^{99m}Tc]MAG_3 and identical data were obtained as outlined above using a general all purpose ^{99m}Tc collimator and a 20% window centered over the 140 keV photon peak of ^{99m}Tc.

Whole kidney and cortical regions of interest (ROIs)

were placed over each kidney and computer generated renogram curves were obtained. Time to peak height was determined for each renogram curve. Statistical analysis was performed using the signed rank test for paired data and the rank sum test for unpaired data.

Clearance Studies

Dual radiopharmaceutical studies were performed simultaneously in eight additional volunteers. Each volunteer received an i.v. injection of 150 μCi of [^{131}I]OIH followed immediately by a 5 mCi i.v. injection of MAG_3. Five-milliliter blood samples were obtained at 3, 6, 9, 12, 15, 20, 25, 30, 40, 50, 60, 90, 120, 150, and 180 min postinjection and plasma and whole blood clearances were obtained based on blood and plasma samples ranging from 0–30 to 0–180 min postinjection. The volunteers voided at 30 min, 2 hr, and 3 hr postinjection and the percent injected dose excreted at each time period was determined. Since this group of volunteers received simultaneous injections and imaging was not performed, no corrections were made for postvoid residuals. Plasma protein binding was also determined at 20, 60, and 120 min postinjection.

RESULTS

Clearance and Volumes of Distribution

There was no statistically significant difference in the mean creatinine values of the two groups. Serum creatinines for the 18 volunteers were obtained within 1 wk of the renal scan and ranged from 0.7 to 1.4 mg/dl (Table 1). Blood samples during the sequential imaging studies were not obtained in two of the volunteers and the [^{99m}Tc]MAG_3 dose was partially infiltrated in a third. In the seven individuals for whom we have comparison data available, the 30-min blood clearance of [^{99m}Tc]MAG_3 was 1.30 ± 0.32 l/min compared with 0.88 ± 0.19 l/min for [^{131}I]OIH, $p \leq 0.05$ (Table 1). In contrast, following simultaneous injection, the 30-min blood clearance of [^{99m}Tc]MAG_3 was less than [^{131}I]OIH, 0.77 ± 0.14 compared with 1.01 ± 0.13 l/min, respectively, $p \leq 0.05$. The mean volume of distribution of MAG_3 (19.3 l) obtained in sequential imaging study was significantly higher than the mean volume of distribution of MAG_3 (8.05 l) following simultaneous injection, $p \leq 0.01$. There was no statistically significant difference between the clearances and volumes of distribution of [^{131}I]OIH following sequential or simultaneous injection.

Following simultaneous injection, both blood and plasma clearances were calculated over multiple time intervals ranging from 0–30 to 0–180 min postinjection. The 0–30-min clearances slightly overestimated the clearances based on longer time periods, but the ratios of plasma/blood clearances for both agents were essentially unchanged (Tables 2A and 2B). The ratios of the [^{99m}Tc]MAG_3/OIH plasma clearance increased slightly

TABLE 1
Serum Creatinine, Blood Clearance (l/min) and Volumes of Distribution (l) of [^{99m}Tc]MAG_3 and [^{131}I]OIH*

Sequential studies	Serum creatinine (mg/dl)	Clearance		Volumes of distribution	
		MAG_3	OIH	MAG_3	OIH
1-S	1.4	2.01	0.98	26.99	17.68
2-E	1.4	1.27	0.84	16.76	14.49
3-R	1.0	1.17	0.59	12.98	3.85
4-Do	1.0	1.14	0.88	14.90	21.76
5-Hn	1.0	1.05	0.92	17.33	13.43
6-Hs	0.9	1.26	0.77	26.71	10.94
7-De	1.2	1.22	1.20	19.49	19.33
8-C	1.0	—	—	—	—
9-B	1.2	—	—	—	—
10-W	1.2	—	—	—	—
Mean ± s.d.	1.13 ± 0.18	1.30 ± 0.32	0.88 ± 0.19	19.31 ± 5.53	14.50 ± 5.96
Simultaneous studies					
1-C	1.1	0.65	0.90	7.66	13.58
2-E	1.0	0.77	1.13	7.50	10.39
3-B	0.9	0.75	0.92	7.51	10.44
4-S	1.2	0.59	0.88	9.99	15.69
5-B	0.7	1.03	0.98	7.98	7.76
6-M	0.9	0.80	0.97	8.74	9.38
7-F	1.1	0.70	1.01	8.30	9.38
8-W	1.0	0.84	1.25	6.73	13.90
Mean ± s.d.	0.99 ± 0.16	0.77 ± 0.14	1.01 ± 0.13	8.05 ± 0.99	10.75 ± 3.55

*For comparison purposes, this table presents 30-min clearance and volumes of distribution based on whole blood samples for both sequential and simultaneous studies.

TABLE 2A
Mean Plasma and Blood Clearances (l/min) of [^{99m}Tc]MAG_3 Measured at Various Time Intervals from 0–30 to 0–180 min Following Simultaneous OIH Injection

Clearance	0–30	0–60	0–90	0–120	0–150	0–180
Plasma	0.45 ± 0.12	0.42 ± 0.12	0.37 ± 0.06	0.41 ± 0.12	0.41 ± 0.13	0.40 ± 0.12
Blood	0.77 ± 0.14	0.73 ± 0.14	0.68 ± 0.09	0.70 ± 0.14	0.70 ± 0.15	0.67 ± 0.13
Ratio of plasma/blood	57%	56%	56%	55%	55%	55%
Volume of distribution						
Plasma	4.92 ± 0.61	5.21 ± 0.59	5.71 ± 0.61	5.33 ± 0.67	5.35 ± 0.67	5.36 ± 0.66
Blood	8.05 ± 0.99	8.55 ± 0.80	9.16 ± 0.81	8.72 ± 0.83	8.72 ± 0.79	8.79 ± 0.83

TABLE 2B
Mean Plasma and Blood Clearances (l/min) of [^{131}I]OIH Measured at Various Time Intervals from 0–30 to 0–180 min Following Simultaneous [^{99m}Tc]MAG_3 Injection

	0–30	0–60	0–90	0–120	0–150	0–180
Plasma	0.65 ± 0.11	0.60 ± 0.10	0.53 ± 0.08	0.56 ± 0.09	0.54 ± 0.08	0.52 ± 0.08
Blood	1.01 ± 0.13	0.94 ± 0.13	0.93 ± 0.17	0.88 ± 0.12	0.85 ± 0.12	0.82 ± 0.12
Ratio of plasma/blood	42%	37%	37%	37%	38%	39%
Volume of distribution						
Plasma	6.33 ± 1.82	7.03 ± 1.68	7.10 ± 1.68	7.20 ± 1.68	7.25 ± 1.62	7.34 ± 1.55
Blood	10.75 ± 3.55	11.04 ± 3.86	12.01 ± 4.15	12.19 ± 2.51	11.82 ± 2.97	12.04 ± 2.95

from 69 ± 19% (0–30 min) to 76 ± 27% (0–180 min) while the ratios of the [^{99m}Tc]MAG_3/OIH blood clearances increased even less, 77 ± 13% (0–30 min) to 84 ± 22% (0–180 min). The slopes and $T_{½}$ values for each of the two components of the blood disappearance curves of simultaneous and sequential studies were not significantly different for either MAG_3 or OIH (Table 3).

Urine Excretion

In the sequential studies, two of ten volunteers were unable to void 30 min after receiving the [^{99m}Tc]MAG_3. Furthermore, timed 3-hr urine collections following OIH administration were not collected. In each of the remaining eight subjects, the 30-min bladder corrected urine excretion of [^{99m}Tc]MAG_3 was greater than that of OIH with a mean value of 73.0 ± 4.2% of the injected dose of MAG_3 excreted by 30 min compared with 66.8 ± 6.1% for OIH (Table 4). By 3 hr, the excretion of MAG_3 was virtually complete (Table 4). Following simultaneous injection, the mean 30-min MAG_3 excretion was 73.1 ± 6.2% compared with 69.6 ± 7.9% for OIH (Table 4); these results are essentially identical to the results of the sequential imaging studies. Technetium-99m MAG_3 excretion from 30–120 min postinjection was 24.2 ± 4.9% compared with 20.9 ± 7.2% for OIH and at 3 hr, excretion of MAG_3 was virtually complete, 99.9 ± 4.3% compared with 93.2 ± 8.5% for OIH. The differences in the 30-min, 2-hr, and 3-hr renal excretion of MAG_3 and [^{131}I]OIH were not significant.

Plasma Protein Binding

In the simultaneous study, plasma protein binding was measured in all eight subjects, at 20 min postinjection; measurements were made again at 60 min (MAG_3, n = 8; OIH, n = 6) and at 120 min (MAG_3 and OIH, n = 3). There was no statistically significant difference in protein binding of MAG_3 at the 20-, 60-, and 120-min time periods, 85.7 ± 2.2%, 88.0 ± 2.0%, and 88.7 ± 3.7%, respectively. Similarly, there was no significant difference in OIH protein binding at the three time

TABLE 3
Compartmental Coefficients and $T_{½}$ of Two Components of Blood Disappearance Curves of OIH and MAG_3 Activity for Sequential (N = 7) and Simultaneous (N = 8) Studies*

		Compartmental coefficients	
	N	1	2
MAG_3	7	0.225 ± 0.050	0.0424 ± 0.007
OIH	7	0.262 ± 0.176	0.0397 ± 0.015
MAG_3	8	0.257 ± 0.065	0.0455 ± 0.008
OIH	8	0.307 ± 0.166	0.0390 ± 0.008
		$T_{½}$	
		1	2
MAG_3	7	3.18 ± 0.8	16.9 ± 2.7
OIH	7	4.34 ± 0.9	15.7 ± 3.0
MAG_3	8	2.90 ± 0.9	15.7 ± 3.0
OIH	8	2.70 ± 1.1	18.4 ± 3.8

* Data are based on 30-min blood samples.

TABLE 4
Urine Excretion (% of Injected Dose) of MAG_3 and OIH During Sequential and Simultaneous Studies

	Sequential studies				Simultaneous studies			
Subject	0–30 MAG_3 excretion	0–30 OIH excretion	3 hr MAG excretion	Subject	0–30 MAG_3 excretion	0–30 OIH excretion	0–180 MAG_3 excretion	0–180 OIH excretion
1-S	79	74	98.0	1-C	64.8	60.9	98.8	98.9
2-E	72	62	99.7	2-E	68.0	77.5	91.2	99.2
3-R	72	71	97.7	3-B	76.7	64.8	100.3	90.6
4-Do	77	68	—	4-S	72.2	73.5	102.5	102.2
5-Hn	65	60	98.3	5-B	76.2	68.1	99.0	86.6
6-Hs	73	68	99.9	6-M	81.8	82.6	101.5	102.6
7-Dc	—	60	99.1	7-F	66.4	60.4	100.0	83.9
8-C	75	73	99.4	8-W	78.7	68.1	106.2	81.5
9-B	71	58	99.2					
10-W	—	67	95.0					
$\bar{X}$	73.0	66.8	98.5	$\bar{X}$	73.1	69.6	99.9	93.2
s.d.	4.2	6.1	1.5	s.d.	6.2	7.9	4.3	8.5

periods, 63.0 ± 5.9%, 64.1 ± 8.3%, and 71.6 ± 6.6%, respectively. The protein binding of [^{99m}Tc]MAG_3 was significantly greater than OIH, $p \leq 0.05$.

Analog Images

[^{99m}Tc]MAG_3 images consistently provided better structural detail of the vessels, kidney, and collecting system than did [^{131}I]OIH (Figs. 2 and 3). Upper abdominal images were obtained in two individuals and there was no evidence of hepatobiliary excretion.

Digital Analysis

There was a computer failure during the data collection of one volunteer. Consequently, the following results describing time to peak height for whole kidney and cortical ROIs based on the nine subjects for whom comparison data are available.

Time to peak height was determined for [^{99m}Tc]MAG_3 and OIH using both whole kidney and cortical ROIs. With whole kidney ROIs, the average time to peak height (207 ± 80 sec) after [^{99m}Tc]MAG_3 injection

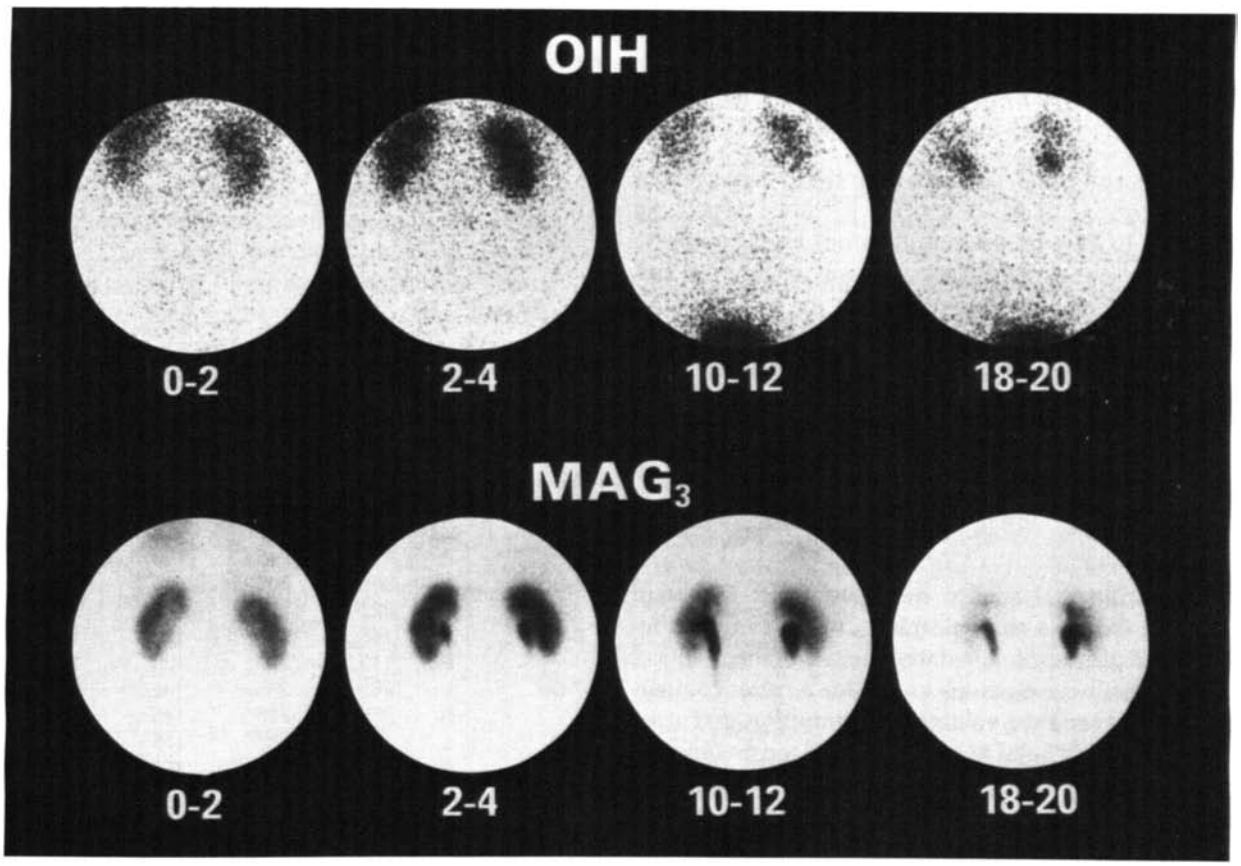


FIGURE 2
OIH and [^{99m}Tc]MAG_3 images for Subject 6 are shown at corresponding time intervals for comparison

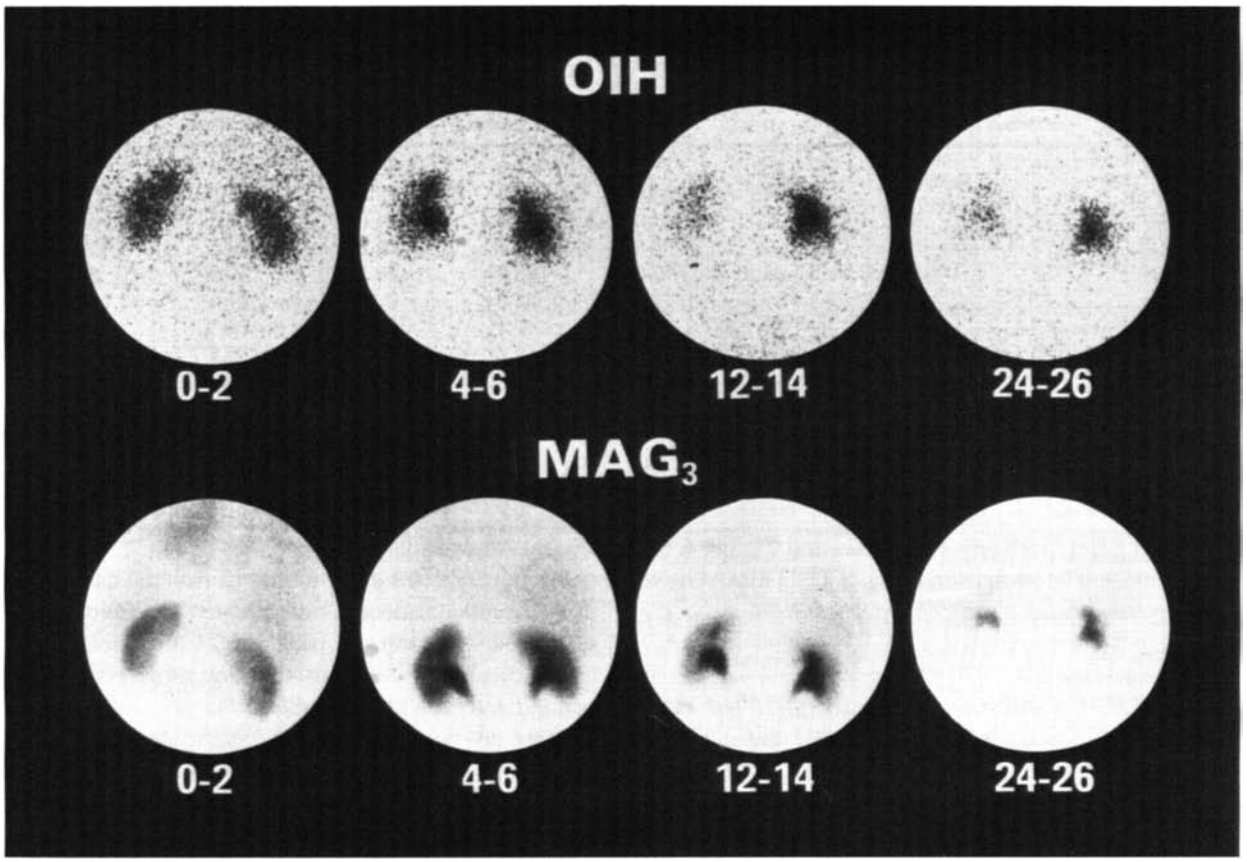


FIGURE 3
OIH and [^{99m}Tc]MAG_3 images for Subject 10 are shown at corresponding time intervals for comparison

was not significantly different from the average time to peak height (223 ± 66 sec) for [^{131}I]OIH (Table 5). Cortical ROIs were selected to avoid artifacts due to pooling of either radiopharmaceutical in the renal collecting system; time to peak height for cortical ROIs was 145 ± 22 sec for [^{99m}Tc]MAG_3 compared with 158 ± 27 sec for OIH (Table 5). These values were not significantly different. The renogram curves for the volunteers in Figs. 2 and 3 are presented in Figs. 4 and 5, respectively.

DISCUSSION

The sequential studies were performed to obtain imaging data as well as clearance, volume of distribution, and urine excretion data. The simultaneous injection studies were obtained to provide a better comparison of the clearance, volumes of distribution, and urine excretion of [^{99m}Tc]MAG_3 and OIH. All the preliminary studies in volunteers comparing [^{99m}Tc]MAG_3 and [^{131}I] OIH were very encouraging, however, an unexpected finding was the observation that the 30-min blood clearance of [^{99m}Tc]MAG_3 was significantly faster than OIH in the sequential imaging studies, 1.30 ± 0.32 l/

TABLE 5
Time (sec) to Maximal Activity [^{99m}Tc]MAG_3 and OIH Using Both Cortical and Whole Kidney Regions of Interest

Subject		Whole kidney ROI		Cortical ROI	
		MAG_3	OIH	MAG_3	ROI
1-S	L	125	125	105	105
	R	125	225	125	225
2-E	L	445	—	187	—
	R	245	—	165	—
3-R	L	185	405	145	165
	R	405	245	165	165
4-Do	L	165	185	165	185
	R	165	245	165	145
5-Hn	L	345	305	185	165
	R	225	285	165	185
6-Hs	L	145	265	125	145
	R	145	205	125	125
7-De	L	285	245	145	125
	R	265	225	145	145
8-C	L	185	185	145	165
	R	285	185	165	165
9-B	L	145	165	125	165
	R	165	205	165	185
10-W	L	145	145	125	145
	R	225	165	125	145
Mean ± s.d.		207 ± 80	223± 66	145 ± 22	158 ± 27

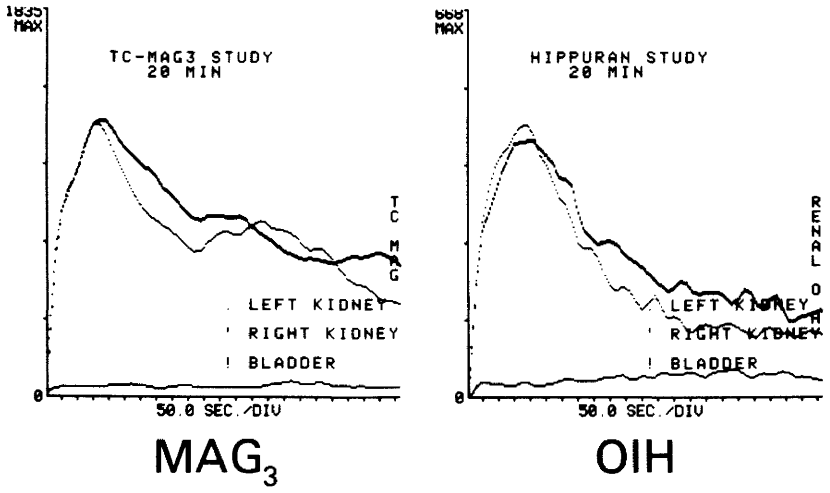


FIGURE 4
Whole kidney renogram curves for Subject 6 (Fig. 2)

min (MAG_3) compared with 0.88 ± 0.17 l/min (OIH) while it was significantly slower than OIH following simultaneous injection, 0.77 ± 0.14 l/min (MAG_3) compared with 1.01 ± 0.13 l/min (OIH). OIH clearance following the simultaneous injection was not statistically different from the OIH clearance following sequential injection; however, the MAG_3 clearance following simultaneous injection decreased significantly compared with the MAG_3 clearance following sequential injection, 1.30 ± 0.32 l/min compared with 0.77 ± 0.14 l/min, $p \leq 0.01$.

An obvious explanation for these differences is the difference in the radiopharmaceuticals used in the two studies. OIH was a commercial preparation and there was no evidence of product failure based on thin layer chromatography or HPLC analysis; furthermore, the OIH clearance was essentially the same in the simultaneous and sequential injection studies. The initial supply of the MAG_3 ligand was exhausted during the sequential studies and a new batch of the ligand had to be prepared for the simultaneous studies. When preliminary results followed simultaneous injection of [^{99m}Tc]MAG_3 and [^{131}I]OIH showed a slower clearance of MAG_3, we resynthesized additional MAG_3 ligand; additional simultaneous injection studies gave the same result, a slower [^{99m}Tc]MAG_3 clearance. All [^{99m}Tc]MAG_3 used in both studies was purified by HPLC. Clearances in rats gave the same results as we had previously obtained and further HPLC analysis under different conditions did not disclose any contaminants in the primary peak. Furthermore, the 30-min urine excretion was essentially the same in both studies. In summary, although the original ligand used in the sequential studies was no longer available, we could not find any evidence to suggest a deterioration in [^{99m}Tc]MAG_3 used in the simultaneous injection study.

Another possible explanation for the difference might lie in the application of the single injection, two-compartmental model (*15,16*). The two-compartmental clearance model was originally applied by Saperstein et al. to 0–60 min blood samples to measure the creatinine clearance in dogs (*15*). Preliminary studies in rats have

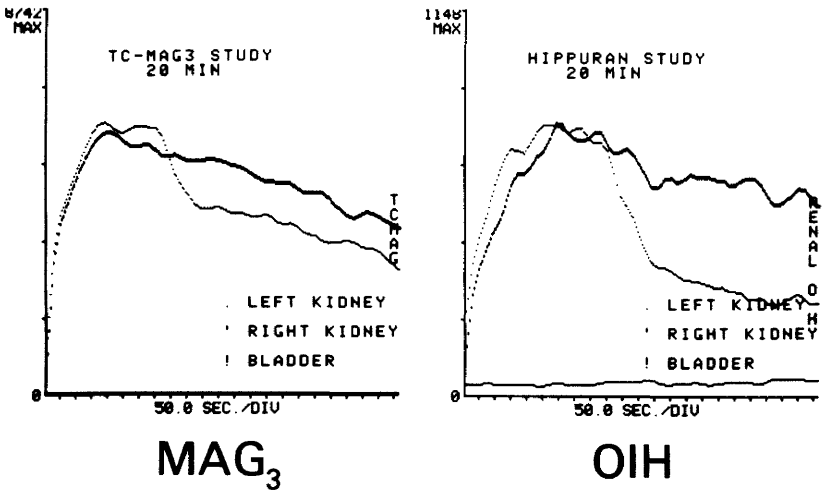


FIGURE 5
Whole kidney renogram curves for Subject 10 (Fig. 3)

shown that there is no significant difference between the [^{99m}Tc]MAG_3 clearances based on the single injection, two-compartment model and constant infusion. Since Saperstein et al. used a 60-min data collection to calculate creatinine clearances and since [^{131}I]OIH clearance is approximately three to four times faster than the creatinine clearance, we made our initial measurements over a 30-min period. Previous investigators have also used data obtained within the first 30 min after OIH injection to calculate a simplified OIH clearance even though 60 min of data collection are preferred to obtain better estimates of each component (*16–18*). Because we were primarily interested in the relative clearances of [^{131}I]OIH and [^{99m}Tc]MAG_3 and needed to minimize time on our clinical instruments, we made our initial measurements over a 30-min period.

Imaging studies were not performed on the subjects receiving simultaneous injections and blood samples were obtained from 3 min to 180 min postinjection. Since ~15% of the blood OIH activity is in the red blood cells, we also calculated both whole blood and plasma clearances for the simultaneously injected OIH and MAG_3. The 30-min OIH and MAG_3 blood and plasma clearances slightly overestimated (and volumes of distribution slightly underestimated) the clearances and volumes of distribution determined over a longer period of time due to poorer definition of the slower component but these differences were minor and there was little change in the ratio of MAG_3/OIH clearances or volumes of distribution obtained at the various time intervals from 30 to 180 min postinjection (Tables 2A and 2B). These results support use of the 30-min clearance and volumes of distribution for comparison purposes.

There were no significant differences in the half-time determinations for either of the two compartments or for the two-compartmental coefficients for [^{99m}Tc]MAG_3 or OIH in the sequential and simultaneous studies (Table 3). The main difference in the two studies was a decrease in the calculated clearance of [^{99m}Tc]MAG_3 that cannot be explained by differences in slopes or half-time clearance values of each compartment.

Urine excretion of [^{99m}Tc]MAG_3 and OIH at 30 min was essentially identical in both studies. At 3 hr, urine excretion of [^{99m}Tc]MAG_3 was essentially quantitative and slightly greater than OIH, 99.9 ± 4.3% compared with 93.2 ± 8.5% although this difference was not statistically significant. The fall in the [^{99m}Tc]MAG_3 clearance in the simultaneous study did not affect the urine excretion because the volume of distribution also decreased. A lower clearance multiplied by a higher blood concentration could give essentially the same urine excretion.

We considered the possibility of an error in the calculations of clearance and volumes of distribution, but each study was internally quite consistent; OIH clearances and volumes of distribution were essentially the same in the two studies and all studies were processed using the same computer and software. Results were no different when a second software program was used to analyze the data.

The possibility that tracer administration of OIH could interfere with the clearance of [^{99m}Tc]MAG_3 needs to be considered. In rats, the clearance of MAG_3 was greater than simultaneously administered OIH (*14*) and concentrations of probenecid of ~2 mg/ml were required to produce a modest 15% decrease in MAG_3 clearance. These results coupled with similar OIH and MAG_3 clearances in a limited series of patients with renal dysfunction (*19*) makes interference of MAG_3 clearance by tracer quantities of OIH highly unlikely.

In the sequential imaging studies, OIH was given first followed by [^{99m}Tc]MAG_3 ~45–60 min later. It is conceivable that the psychologic stress of placing two i.v. lines, injecting radioactivity, and imaging with a gamma camera resulted in a catecholamine release causing a decrease in renal blood flow at the time [^{131}I]OIH was administered followed by a rebound phenomenon by the time MAG_3 was administered approximately an hour later when the volunteer was relaxed and comfortable with his surroundings. An increase in clearance would be expected to be associated with an increase in urine excretion but a 30-min urine collection may not have been early enough to detect the difference. (For example, following a bolus injection, the 24-hr excretion of [^{99m}Tc]DTPA and OIH are essentially identical but there are major differences in the 30-min excretion).

We do not feel the differences in the clearance values obtained for [^{99m}Tc]MAG_3 in the sequential and simultaneous studies have been adequately explained and we plan to perform simultaneous constant infusion studies using [^{99m}Tc]MAG_3 and OIH to try to resolve this question. In summary, [^{99m}Tc]MAG_3 appears to be a strong candidate as a ^{99m}Tc replacement for OIH. Technetium-99m MAG_3 clearance is quite rapid, the renogram curves are very similar to those obtained with OIH, and the 30-min urine excretions are essentially identical. Finally, single injection 30-min clearance data can be used to obtain valid comparisons of [^{131}I]OIH and [^{99m}Tc]MAG_3.

FOOTNOTES

* Mallinckrodt Inc., St. Louis, MO and Medi-Physics, Inc., Richmond, CA.

† Baker Chemical Co., Phillipsburg, NJ.

‡ Technicare Corp. (560), Solon, OH.

ACKNOWLEDGMENTS

The authors acknowledge support from Mallinckrodt, Inc., and Department of Energy contract number 83ER60140, and NIH Grant # R01 AM 33692-01A1. They also thank Jeff Fox,

PhD, for the use of his computer program used in our curve stripping analysis. Also acknowledged are Joan Salm's assistance in preparing the manuscript and Dr. James Reading's assistance with the statistics.

REFERENCES

1. Klopper JF, Hauser W, Atkins HL, et al: Evaluation of ^{99m}Tc-DTPA for the measurement of glomerular filtration rate. *J Nucl Med* 8:77–85, 1972
2. Barbour GL, Crumm CK, Boyd CM, et al: Comparison of inulin, iothalamate, and ^{99m}technetium DTPA for measurement of glomerular filtration rate. *J Nucl Med* 17:317–320, 1976
3. Taylor AT: Quantitative renal function scanning: A historical and current status report on renal radiopharmaceuticals. In *Nuclear Medicine Annual 1980*, Freeman LM, Weissmann HS, eds. New York, Raven Press, 1980, pp 303–340
4. McAfee JG, Grossman ZD, Gagne GR, et al: Comparison of renal extraction efficiencies for radioactive agents in the normal dog. *J Nucl Med* 22:333–338, 1981
5. Stadalnik RC, Vogel JM, Jansholt A-L, et al: Renal clearance and extraction parameters of ortho-iodohippurate (I-123) compared with OIH (I-131) and PAH. *J Nucl Med* 21:168–170, 1980
6. Marcus CS, Kuperus JH: Pediatric renal I-123 orthoiodohippurate dosimetry. *J Nucl Med* 26:1211–1214, 1985
7. Scharf SC, Blaufox MD: Radionuclides in the evaluation of urinary obstruction. *Semin Nucl Med* 12:254–264, 1982
8. Davison A, Jones A, Orvig C, Sohn M: A new class of oxotechnetium (+5) chelate complexes containing a $TcON_2S_2$ core. *Inorg Chem* 20:1629–1632, 1981
9. Fritzberg AR, Klingensmith WS, Whitney WP, et al: Chemical and biological studies of Tc-99m N,N′-bis(mercaptoacetamido)-ethylenediamine: A potential replacement for I-131 hippuran. *J Nucl Med* 22:258–263, 1981
10. Klingensmith WC III, Gerhold JP, Fritzberg AR, et al: Clinical comparison of Tc-99m N,N′-bis-(mercaptoacetamido)-ethylenediamine and [^{131}I]ortho-iodohippurate for evaluation of renal tubular function: Concise communication. *J Nucl Med* 23:377–380, 1982
11. Fritzberg AR, Kuni CC, Klingensmith WC et al: Synthesis and biological evaluation of Tc-99m N,N′-bis(mercaptoacetyl)-2,3-diaminopropanoate: A potential replacement for (I-131)-o-iodohippurate. *J Nucl Med* 23:592–598, 1982
12. Klingensmith WC, Fritzberg AR, Spitzer VM, et al: Clinical evaluation of Tc-99m N,N′-bis-(mercaptoacetyl)-2,3-diaminopropanoate as a replacement for I-131 hippuran. *J Nucl Med* 24:P80, 1983 (abstr)
13. Chervu RL, Sundoro BM, Blaufox MD: Technetium-99m labeled p-aminohippuric acid analog: A new renal agent: Concise communication. *J Nucl Med* 25:1111–1115, 1984
14. Eshima D, Fritzberg AR, Kasina S, et al: Comparison of a new Tc-99m renal function agent, Tc-99m mercaptoacetyltriglycine with I-131 OIH. *J Nucl Med* 26:P56–57, 1985 (abstr)
15. Sapirstein LA, Vidt D, Mandel M, et al: Volumes of distribution and clearances of intravenously injected creatinine in the dog. *Am J Physiol* 181:330, 1955
16. Blaufox MD, Potchen EJ, Merrill JP: Measurement of effective renal plasma flow in man by external counting methods. *J Nucl Med* 8:77–85, 1967
17. Blaufox MD, Merrill JP: Simplified hippuran clearance. *Nephron* 3:274–281, 1966
18. Ram MD, Evans K, Chesholm GD: A single injection method for measurement of effective renal plasma flow. *Br J Urol* 40:425–428, 1968
19. Taylor A, Eshima D, Fritzberg AR, et al: Evaluation of Tc-99m mercaptoacetyltriglycine as a potential replacement for I-131 hippurate in human subjects. *J Nucl Med* 26:P57, 1985 (abstr)