Technetium-99m MAG_3, A Comparison with Iodine-123 and Iodine-131 Orthoiodohippurate, in Patients with Renal Disorders

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A Phase I study in 12 patients with renal disorders compared the simultaneous clearances of ^{99m}Tc-labeled mercaptoacetyltriglycine (MAG_3) and ^{131}I-labeled orthoiodohippurate (OIH). The ratio of MAG_3 to OIH clearance was 0.61 ± 0.08 as a result of its smaller volume of distribution, ratio 0.65 ± 0.09, for the clearance half-lives were similar, ratio 1.09 ± 0.12. A Phase II study performed serially in 20 patients with equal doses of [^{99m}Tc]MAG_3 and [^{123}I]OIH gave images of equal quality. The relative renal functions were highly correlated ($r = 0.97$, $p < 0.001$) and transit time analyses gave good correlations: parenchymal transit time index $r = 0.81$, $p < 0.05$. We conclude that [^{99m}Tc]MAG_3 has some advantages over [^{99m}Tc]DTPA and is a suitable replacement for [^{123}I]hippuran in routine renal imaging, relative function, and transit time studies, but not for the accurate estimation of the renal plasma flow.

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Classic renal physiology emphasizes the difference between glomerular filtration and tubular function. The traditional compounds for the assessment of these parameters were inulin and para-amino hippurate (PAH), respectively. These were replaced by chromium-51-labeled EDTA and iodine-131- (^{131}I) labeled ortho iodohippurate (hippuran, OIH), that in turn were replaced by technetium-99m diethylenetramine pentaacetic acid ([^{99m}Tc]DTPA) and [^{123}I]OIH.

Technetium-99m DTPA has excellent physical properties for imaging and gives a low radiation dose to the patient. Because it is cleared by glomerular filtration, its renal extraction efficiency is only 20% (the filtration fraction). This may result in a low target to background ratio and nondiagnostic images in patients with impaired renal function.

Orthoiodohippurate is labeled with ^{131}I or iodine-123 (^{123}I). Its renal handling is intimately understood and its higher extraction efficacy, 87% (*1*), is extremely useful, especially in evaluation of patients with poor renal function and in some sophisticated data processing. The use of ^{131}I to label hippuran is rather undesirable. It gives a large radiation dose to the patient in the presence of outflow obstruction (*2*) and there is poor spatial resolution and sensitivity on imaging, the permissable administered dose being limited, and the photon energy being too high for efficient detection with the conventional gamma camera. The use of ^{123}I itself, is quite suitable (gamma-ray energy 159 keV; half-life 13.2 hr), but there are practical disadvantages. This cyclotron-produced radionuclide is relatively expensive and if produced by a low-energy cyclotron reaction it contains iodine-124 (^{124}I) that increases the radiation dose and reduces image quality. Its availability is limited, reducing its applicability in routine clinical use. These problems have led to the search for some suitable agent of comparable efficiency that could be labeled with ^{99m}Tc and used for renal studies.

In 1979, Davidson and co-workers (*3*) introduced a new class of chelating agents for technetium that were based on amide nitrogen and thiolate (N_2-S_2 ligands)

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and that behaved similarly to orthoiodohippurate in renal studies in animals. Subsequently, derivations (Tc-DADS) were synthesized and evaluated (*4–8*) and alternative agents (*9–11*) were investigated, summarized by Taylor et al. (*12*).

Most recently, a new N_3-S ligand, mercapto-acetyl triglycine (MAG_3) has been proposed as a potential ^{99m}Tc replacement for IOIH in animal experiments (*11*). Its chelation with ^{99m}Tc resulted in a single radiochemical product and its excretion rate was found to be faster than that of OIH in normal as well as probenecid treated animals. In another study by Taylor et al. (*12*), its clearance and imaging has been compared with that of [^{131}I]hippuran in normal volunteers.

We have carried out a comparative study of MAG_3 and hippuran in patients with varying degrees of renal function impairment in two phases. The first phase was to compare the simultaneous renal clearance of ^{99m}Tc-labeled MAG_3 and ^{131}I-labeled hippuran in such patients and in the second phase we performed serial renal radionuclide studies with a computer-linked gamma camera using both [^{99m}Tc]MAG_3 and ^{123}I-labeled hippuran and compared the analog images obtained and various other more sensitive parameters to evaluate renal function.

MATERIALS AND METHODS

Patients were selected for both phases through their willingness to undertake the study from those referred to our department for renal investigations. The majority came from the Hypertension Clinic and the Urology Department at St Bartholomew's Hospital, London. The study was acceptable to the City & Hackney District Ethical Committee and to the Administration of Radioactive Substances Committee. The procedure was explained to the patients and written informed consent was obtained.

Phase I Methodology: Dosage Preparation

Technetium-99m MAG_3. MAG_3 was supplied commercially* in the form of white powder in sealed glass vials (Code MP600). A lead-shielded water bath was prepared and brought to the boil. About 5 mCi (185 MBq) of [^{99m}Tc]O_4 was eluted in the standard way from a technetium generator (Code UTK).* Volume dilution of the pertechnetate stock to give the required activity was only with physiologic saline. An amount was calculated so that the volume to be added to the vial of MAG_3 was not < 4 ml and not more than 10 ml. The vial was then placed in the boiling water bath and left there for 10 min. Then it was removed and cooled under running tap water or by immersion in cold water.

Iodine-131 hippuran. Iodine-131 hippuran was obtained commercially† and it was of the quality especially made for the measurement of effective renal plasma flow (ERPF). The amount of the activity in the vial was ~ 500 μCi (18.5 MBq) in 10 ml.

Patient dose. The two radiopharmaceuticals were mixed to ensure simultaneous injection and about one-tenth of the total volume was withdrawn into a weighed syringe. The dose proposed for the patient was ~ 0.5 mCi (18.5 MBq) of [^{99m}Tc]MAG_3 and 50 μCi (1.85 MBq) of [^{131}I]OIH. In retrospect a technique for simultaneous injection avoiding mixture of the two radiopharmaceuticals might be preferable.

Procedure

The patient lay on a comfortable bed. An i.v. cannula was put into a suitable arm vein with a three-way connector for taking blood samples and flushing. After injecting the dose to the patient, blood samples were taken at 2.5, 5, 7.5, 10, 15, 20, 30, 60, and 90 min postinjection. At each time a small blood sample was discarded before the 5-ml sample was taken for analysis. An approximately equal volume of the plasma obtained from these samples was put into weighted tubes which were re-weighed to determine the exact amount of plasma in each tube. Whole plasma not an ultra-filtrate was used since in vivo it is whole plasma that is available to the renal tubules.

Counting

For counting, the following standards were prepared at the time of dose preparation. These were: (a) [^{99m}Tc]MAG_3 counting standard; (b) [^{131}I]hippuran counting standard; and (c) injection counting standard.

Counting of the standards, plasma samples, and washings was done in a dual-channel counter after properly calibrating the equipment.

Data Analysis

The data obtained from the counter was then analyzed after performing the corrections for decay, background, and the weight of the sample. As both hippuran and MAG_3 are mainly secreted by the renal tubules, their clearance can be calculated as for the ERPF.

The simplest formula used to calculate ERPF is:

$$ERPF = \frac{\bar{D} \cdot \lambda}{P_0}$$

where: $\bar{D}$ = Total dose injected
λ = Slope of the slow component of clearance curve = $0.693/T_{½}$
P_0 = Plasma concentration at time zero, T_0
$T_{½}$ = The half-time of clearance.

We also calculated ERPF by applying the technique proposed by Nimmon et al. (*13*) for bi-exponential analysis of the clearance curves. This technique gives a more accurate estimate of the values, since it uses the area under the curve including all the data points and gives estimates of the errors in the analysis. Ratios for values of [^{99m}Tc]MAG_3 to [^{123}I]OIH were calculated for each pair with s.d. and s.e.m. using (n − 1) number of observations.

Phase II Methodology: Dosage Preparation

Technetium-99m MAG_3. About 10 mCi (370 MBq) of [^{99m}Tc]pertechnetate was added into the vial containing

MAG_3. The vial was placed into a boiling water bath for 10 min and then cooled under water. The patient dose was ~ 2.5 mCi (92.5 MBq), that was drawn out from the vial.

Iodine-123 hippuran. Iodine-123 hippuran used was obtained from either of two commercial sources.*† The patient dose was ~2.5 mCi (92.5 MBq). The preparations contained < 2% free ^{123}I, < 0.05% ^{125}I and no ^{124}I since it was made by the (p, 5n) reaction. Chromatographic quality control was undertaken to confirm these low levels of free ^{123}I and absence of iodobenzoate.

Technetium DTPA. [^{99m}Tc]DTPA was prepared according to the manufacturer's instructions.* The patient dose was ~10 mCi (370 MBq) as for our routine renal radionuclide studies.

Procedure

The renal radionuclide studies were undertaken with each agent separately 3–150 hr apart. In 15 patients MAG_3 was given before OIH and in five vice versa.

The patient was seated comfortably in a dental chair, reclining with the gamma camera detector head under the back, covering the region including the kidneys and heart. The radiopharmaceutical was injected via a three-way connector to a butterfly line and flushed with saline. The data was collected in the form of analog images at 30 sec, 60 sec, 90 sec, 120 sec, 5 min, 10 min, 15 min, 20 min, 25 min, and 30 min after the injection, and also acquired in 10-sec frame mode by the computer (Nodecrest V76) linked to the camera (IGE 400AT) that was fitted with a general purpose parallel hole collimator designed for energies up to 200 keV. Before and after each study, vital signs were monitored. Blood was taken for a full blood count, urea, creatinine and electrolytes, uric acid and liver function tests before the study and 1 to 3 days later, for safety evaluation.

Preliminary dosimetry calculations show 8 mrad/mCi to the whole body and 12 mrad/mCi both to the normally functioning kidney and to the ovary (bladder emptied at 2 hr). An effective whole-body dose equivalent is calculated at 0.5 mSV per study using 2.7 mCi (100 MBq).

Data Analysis

The data were displayed in a 64 × 64 matrix on a high quality video monitor. Regions of interest were set over the left ventricle (from an early frame), over the renal areas (using the frames ~ 2 min, i.e., before any tracer has left the parenchyme to enter the pelvis), and over the renal background areas identified superior and medial to each kidney avoiding the region of the central vessels. From these renal and background images relative renal function as a percentage left/(left + right) are calculated from the relative quantity of activity in each kidney from 2 min until a time before any activity was lost from a kidney (*14*). The normal range is 50 ± 7%.

The whole-kidney transit time (WKTT) was determined by deconvolution analysis of the activity-time curve from the left ventricle with the activity-time curve from the whole kidney. To obtain the mean parenchymal transit time, first all contributions from the calyces and pelvis must be removed from the renal image so that an activity-time curve from "pure" parenchyme may be used for deconvolution analysis with the left ventricular activity-time curve. This was undertaken by the creation of a mean time functional image of the whole kidney using the activity-time curves from each individual pixel. The time components of data from pixels from calyces or pelvis are at least 100 sec longer than those from pixels from parenchyme because the minimum time for activity to traverse the length of the nephron is 100 sec. On scaling this functional image appropriately, the parenchymal region was easily visualized and separated from the pelvicalyceal region (*14*). Deconvolution analysis yielded an impulse retention function which gave the mean parenchymal transit time, MPTT. This may be divided into a portion representing the minimum transit time, MinTT, of the nephrons which is common to all nephrons, and the residual transit times, the mean of which is called the parenchymal transit time index, PTTI. Thus MPTT = Min TT + PTTI. The minimum transit time represents the minimum obligatory time taken for activity to traverse the length of the nephrons and collecting ducts, and particularly for the latter, depends on the medullary concentrating ability and thus the urine flow (*15*). By correcting both the MPTT and the WKTT for this minimum transit time, narrower normal ranges are obtained for the parenchymal and whole kidney transit time indices and this reduces the effect of interpatient variation in hydration and in urine flow (*16*). The whole kidney transit time index, WKTTI is given thus: WKTTI = WKTT − Min TT. The normal ranges are: for PTTI, 10–156 sec; MPTT, 100–270 sec; and WKTTI 20–170 sec. The difference between WKTTI and PTTI gives the pelvic transit time that is prolonged as a result of mixing and eddying when the pelvis is dilated, whether or not there is a resistance to outflow due to obstructing uropathy.

The response to furosemide was conventionally interpreted as indicating obstructing uropathy when there was no change in the rising activity-time curve. A rapid fall in a rising whole kidney activity-time curve demonstrated the absence of an obstructing uropathy and in addition there was a gray area of partial responses. Difficulties in interpretation arose when renal function was reduced.

Statistical Analysis

Analysis was performed using the Student paired t-test or conventional regression analysis to give the correlation coefficient, r. A "p" value of < 0.05 was taken as significant and of < 0.01 as highly significant.

Summary of Phase II Analyses

1. Visual analysis of analog images.
2. Computer analysis of data. (a) Relative contribution to the total renal function by each kidney. (b) Activity-time curves. (c) Response to furosemide if given. (d) Parenchymal transit time index. (e) Whole kidney transit time index. (f) Mean parenchymal transit time.

RESULTS

Phase I

Renal clearance of ^{99m}Tc-labeled MAG_3 and ^{131}I-labeled hippuran was compared after simultaneous administration in 12 patients with varying degrees of renal function impairment. The clearance values obtained for MAG_3 were found to be ~ 61% of those obtained for hippuran. The values ranged from *58 ml to 550 ml* for MAG_3 and *108 to 798 ml* for hippuran. These

measurements of renal clearance depend upon the volume of distribution of the agent and the rate of clearance ($T_{½}$ of clearance curve).

The study showed that the clearance values were persistently overestimated when the data was analyzed using only the slow component of the bi-exponential clearance curve rather than the whole area under the curve proposed by Nimmon et al. (*13*). The latter method gives a more accurate estimate of the clearance, and was used for the comparisons (Table 1).

The ratio of MAG_3/hippuran clearance was 0.61 ± 0.08 (± 1 s.d.), the ratio of the first component of the clearance half-lives was 1.15 ± 0.23, the ratio of the slow component of the clearance half-lives was 1.09 ± 0.12, and the ratio of the volumes of distribution was 0.65 ± 0.09.

No adverse reactions or significant changes in blood chemistry or blood counts occurred.

Phase II

The comparison of the analog image series and other more sensitive parameters was performed using ^{99m}Tc-labeled MAG_3 and ^{123}I-labeled hippuran administered separately in 20 patients, the interval being within 3 hr to 7 days apart.

The images obtained looked quite similar. Both the agents provided much better details of the kidneys with higher target to background ratios than in four patients where we also obtained images with [^{99m}Tc]DTPA. The images with MAG_3 also showed slight hepatic uptake, which was unrelated to the level of renal function.

The analysis of the transit times showed good correlation. Analysis of PTTI showed a correlation coefficient of 0.81 ($p < 0.05$) and WKTTI a correlation coefficient of 0.92 ($p < 0.01$). The comparison of relative contribution of each kidney to the total renal function gives an even better correlation of $r = 0.97$ ($p < 0.001$).

The renogram curves obtained with the two agents looked quite similar with a correlation of $r = 0.95$ for the comparison of the peak times of the activity curves. [^{99m}Tc]MAG_3 was 240 ± 50 sec, and for [^{123}I]OIH was 240 sec ± 61 sec (1 s.d.).

Four case histories from the 20 patients are given to illustrate the images and activity-time curves from the two compounds (administered dose 2.5 mCi) in a range of conditions. These are contrasted with those from the use of 10 mCi (370 MBq) [^{99m}Tc]DTPA in two cases.

Case 1

A 72-yr-old male with a past history of peritonitis presented with a recent onset of hypertension. Initially the supine blood pressure was 210/85 falling to 150/80 on a combination of a beta-blocker and a diuretic. He then developed nausea, a bad taste in the mouth and weight loss as a result of increasing renal impairment, creatinine clearance 17 ml/min. Both ultrasound studies and i.v. urography showed bilateral hydronephroses. A series of renal radionuclide studies were performed with [^{99m}Tc]DTPA and [^{99m}Tc]MAG_3 (Fig. 1), and [^{123}I] OIH. The activity-time curves are shown for [^{99m}Tc] MAG3 and [^{123}I]OIH in Fig. 2.

The relative function of the left kidney was 55% (right 45%) and both kidneys showed prolonged parenchymal transit time indices of 164 and 165 sec for MAG_3 and 191 and 195 sec for OIH (normal < 156 sec); prolonged WKTTI of 385 and 344 sec for MAG_3 and 379 and 313 sec for OIH giving pelvic transit times of 221 and 179 sec for MAG_3 and 188 and 118 sec for OIH, respectively; and prolonged mean transit times, Table 2, confirming the presence of bilateral obstructive nephropathy. Transurethral prostatectomy lead to some improvement in renal function.

Case 3

A 24-yr-old female had a left pyeloplasty performed in 1975 for pelviureteric junction obstruction. She remained well until early 1986 when she started having recurrent pain in the left loin. Her intravenous urography was reported as showing "recurrent partial left pelviureteric junction obstruction in a previous pyeloplasty". Her renal radionuclide images from [^{99m}Tc] MAG_3 are shown in Fig. 3 and from [^{123}I]OIH in Fig. 4. Pelvicalyceal retention of tracer is seen in the left kidney. The responses to furosemide are good and demonstrated in the activity time curves (Fig. 5). The results of the parenchymal transit time indices and mean transit times are normal in both studies (Table 2), confirming the absence of obstructive nephropathy on the left side. The prolonged WKTTI indicate the delayed transit of tracer through the pelves particularly on the left side. On these results she continues to be treated conservatively.

Case 8

A 63-yr-old man had a 5-yr history of hypertension that was difficult to control and impaired renal function, creatinine clearance 41 ml/min, [^{51}Cr]EDTA clearance was 49 ml/min. He was referred for assessment of possible renovascular disorder. Technetium-99m DTPA, [^{99m}Tc]MAG_3, and [^{123}I]OIH studies showed a very poorly functioning left kidney, having 2% to 3% of the total function. Images from MAG_3 and OIH were similar (Fig. 6). These observations are reflected in the activity-time curves, which for the left kidney for MAG_3 and OIH were slow rising, suggesting renovascular disorder but this was not determinable from the DTPA study (Fig. 7). Transit times were not analyzable on the left side and were normal on the right side (Table 2).

On i.v. urography, the left kidney was hardly visualized but with an upper pole mass, shown to be cystic

TABLE 1
Comparison of Clearances, $T_{½}$ and the Volumes of Distribution of MAG_3 and Hippuran

Patient case no.	MAG_3 Fast component (min)	MAG_3 Slow component (min)	MAG_3 Vol. of distribution (mls)	MAG_3 Clearance (ml/min)	Hippuran Fast component (min)	Hippuran Slow component (min)	Hippuran Vol. of distribution (mls)	Hippuran Clearance (ml/min)
1	4.7	24.5	12285	262	4.0	22.5	22311	493
2	5.1	23.9	24984	550	4.8	25.1	39371	798
3	5.8	33.0	26148	350	4.4	26.2	38503	693
4	4.6	28.2	12439	242	3.6	27.6	24604	476
5	4.6	40.2	12548	198	4.1	35.8	15973	289
6	4.1	31.6	16034	284	5.5	31.9	22759	421
7	4.5	56.2	15610	181	4.4	42.7	18548	278
8	3.6	28.8	20054	408	3.0	27.1	31567	661
9	5.7	28.6	14024	284	3.6	32.4	21438	367
10	5.3	28.0	14614	286	5.5	25.2	24191	519
11	4.8	24.5	17798	398	5.3	22.7	28737	663
12	6.9	73.0	6680	58	4.7	61.0	10523	108

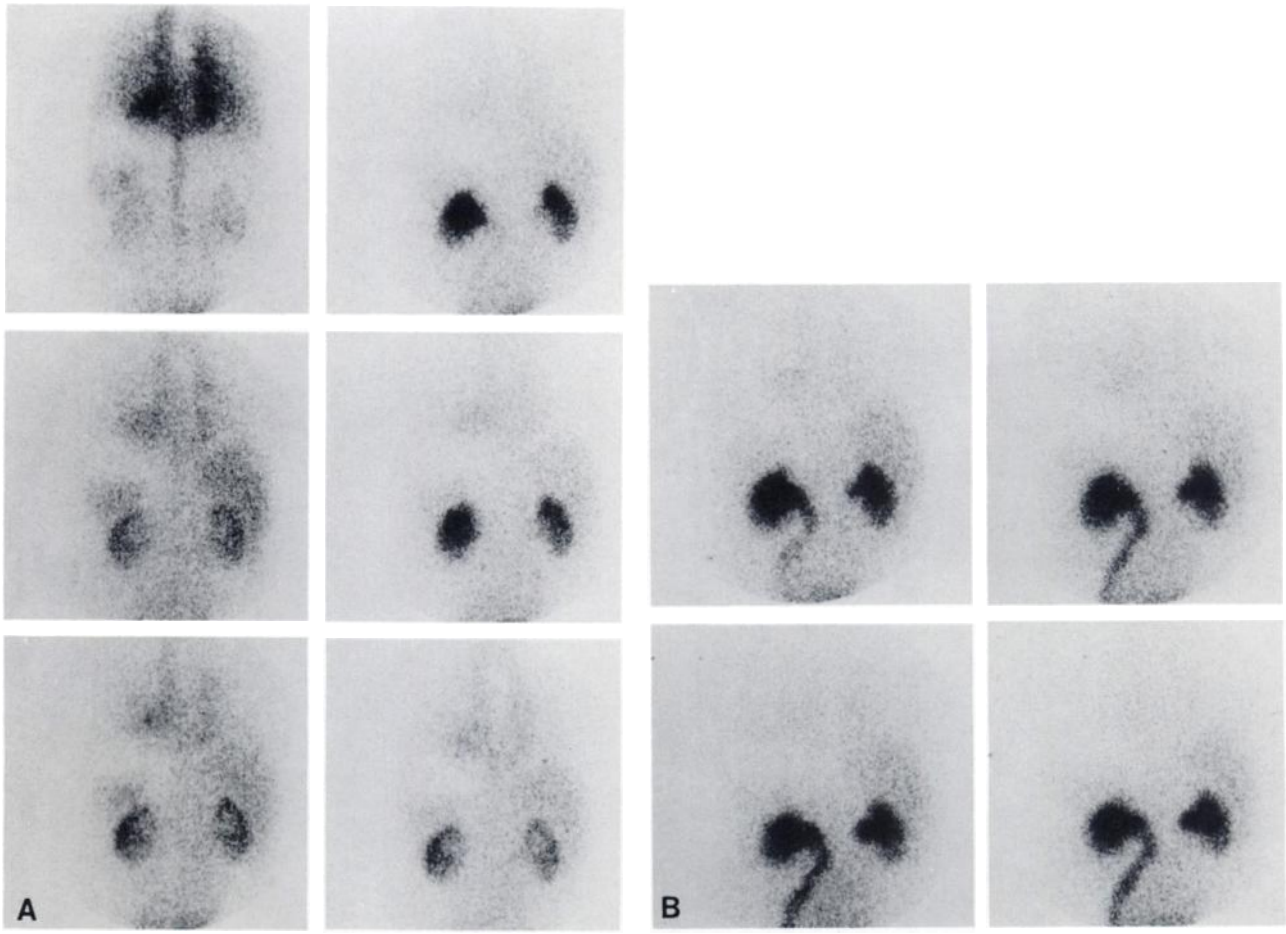

FIGURE 1
[^{99m}Tc]MAG_3 study in Case 1. Bilateral obstructive nephropathy. A: Left-hand images at times 0–30 sec top, 30–60 sec middle, 60–90 sec bottom; right-hand images 90–120 sec bottom, 4.5–5 min middle, 9.5–10 min top. B: Top row images, left 14.5–15 min, right 19.5–20 min; bottom row, left 24.5–25 min, right 29.5–30 min.

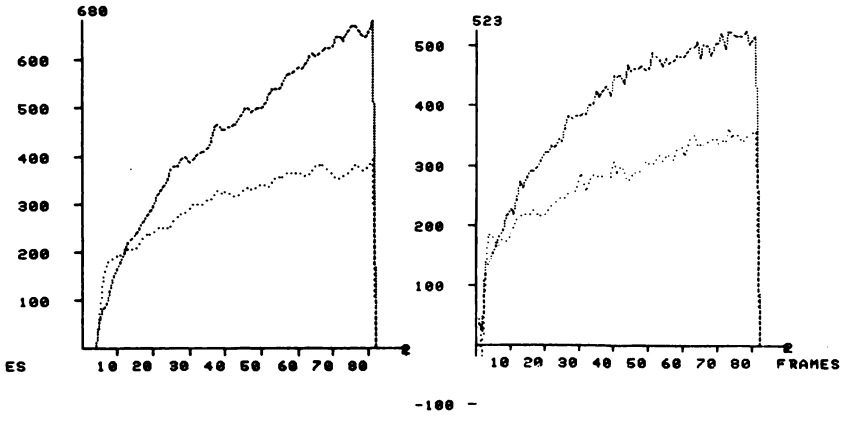

FIGURE 2
Bilateral obstructive nephropathy. Activity-time curves in Case 1. [^{99m}Tc]MAG_3 on the left, [^{123}I]OIH on the right; vertical scale counts/sec, horizontal scale frame rate 20 sec per interval (200 sec = 10); graphs points at 20-sec intervals, left kidney in the darker shade, the upper curve.

on ultrasound and aspirated without benefit to his hypertension. Angiography showed an absent left renal artery with only collateral arterial supply to the left kidney and normal right-sided vessels. Plasma renin activity was elevated. The left renal venous renin concentration was four times that on the right side. Renin output from the left kidney determined from the flow and arterio-venous differences was 1.35 times that from the right kidney. The patient continued to be managed conservatively.

Case 9

A 36-yr-old man with a 2-yr history of mild hypertension was referred for evaluation for possible reno-

TABLE 2
Comparison of Results from [^{99m}Tc]MAG_3 and [^{123}I]OIH in Four Clinical Cases

Patient case no.	Radiopharmaceutical		Time-to-peak renogram curve (min)	Relative renal function (%)	Transit times (sec) PTTI	WKTTI	MPTT	Result/remarks
1	MAG_3	L	No peak	55	164	385	224	Bilateral obstructive nephropathy
		R		45	165	344	265	
	HIPP	L	No peak	54	191	379	271	Bilateral obstructive nephropathy
		R		46	195	313	295	
3	MAG_3	L	5.1	46	104	446	184	No evidence for obstructive nephropathy
		R	5.0	54	101	238	181	
	HIPP	L	7.6	47	60	436	120	No evidence for obstructive nephropathy
		R	7.5	53	36	229	156	
8	MAG_3	L	No peak	2	—	—	—	Very small nonfunctioning left kidney
		R	4.4	98	109	124	209	
	HIPP	L	No peak	3	—	—	—	Very small nonfunctioning left kidney
		R	5.0	97	63	144	183	
9	MAG_3	L	4.0	54	52	117	152	Normal results
		R	4.0	46	42	101	162	
	HIPP	L	3.8	53	78	158	158	Normal results
		R	3.8	47	43	98	163	
Normal values:			3–5 min	50 ± 7%	< 156	< 170	< 270	

vascular disorder. Normal [^{99m}Tc]MAG_3 studies (Fig. 8) and [^{123}I]OIH studies, transit times (Table 2), and activity-time curves (Fig. 9) confirmed the absence of renovascular disorder.

DISCUSSION

The purpose of this study was to evaluate further a new agent for renal studies, i.e., MAG_3 (mercapto-acetyl triglycine) that is labeled with ^{99m}Tc and proposed as a substitute for hippuran. Hippuran is considered the best agent for renal studies and especially when the renal function is impaired. A trial of this new agent in human normal volunteers has been published by Taylor et al. (*12*) showing similar results in comparison with [^{131}I] hippuran (*8*).

Our comparison was undertaken in patients with a variety of degrees of renal function impairment. Iodine-123-labeled hippuran was used instead of ^{131}I-labeled hippuran for these renal studies to give a more realistic and practical comparison with the technetium-labeled agents.

The ideal requirements for any ^{99m}Tc-labeled substitute for hippuran as described by Britton (*17*) can be applied to the findings with [^{99m}Tc]MAG_3. The first requirement is that the compound must not be fixed to renal tissue. This can be evaluated by comparing the peaks of the activity-time curves and the analyses of the transit times. The times to peak for MAG_3 and for hippuran in the study of 20 patients show a significant correlation, $r = 0.95$, and the analyses of the PTTI show a significant correlation, $r = 0.81$, and of the WKTTI, a highly significant correlation, $r = 0.92$. Thus, MAG_3 meets this criteria as a substitute for hippuran to an acceptable degree. The study by Taylor et al. (*2*) has also shown values for average time to peak height in normal volunteers which are not significantly different from those for hippuran. Their values were 207 ± 80 sec for [^{99m}Tc]MAG_3 and 223 ± 66 sec for [^{131}I]OIH when using the whole kidney ROI. In this study they

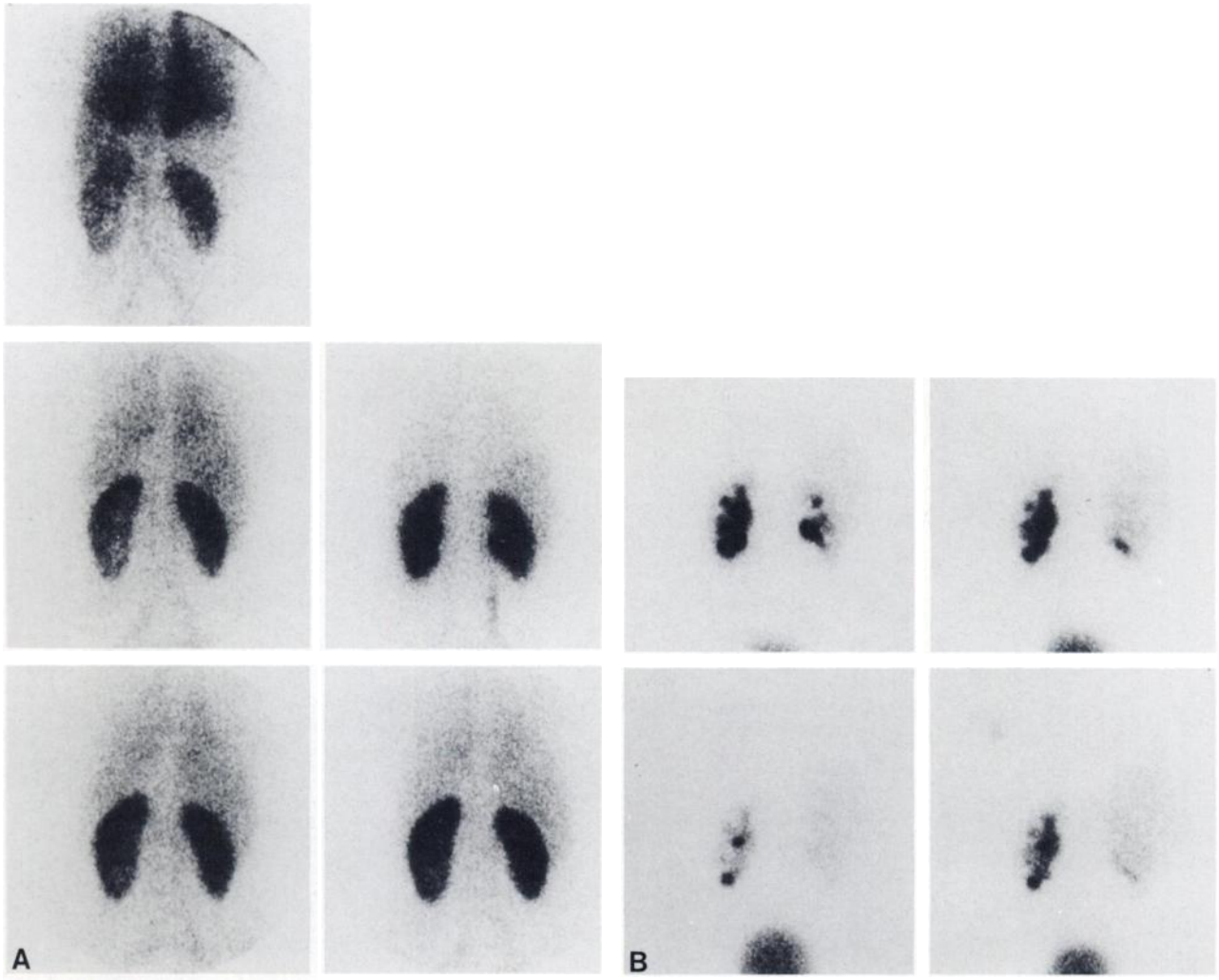

FIGURE 3
[^{99m}Tc]MAG_3 studies in Case 3. Left nonobstructive hydronephrosis. A: Left-hand images at times 0–30 sec top, 30–60 sec middle, 60–90 sec bottom; right-hand image 90–120 sec bottom; 4.5–5 min middle, 9.5–10 min damaged-omitted. B: Top row images, left 14.5–15 min, right 19.5–20 min; bottom row, left 24.5–25 min, 29.5–30 min. Furosemide given at 18 min.

were 209 ± 26 sec for [^{99m}Tc]MAG_3 and 204 ± 30 sec for [^{123}I]OIH (± 1 s.d.) in the 20 apparently normal kidneys.

Another criterion is that the ^{99m}Tc substitute should have an extraction efficiency of over three times that of [^{99m}Tc]DTPA, in order to obtain a significant advantage in signal to noise ratio and to make a clinically evident difference. MAG_3 just about reaches this criterion. A study in rats (*11*) showed an extraction efficiency of ~ 87% for MAG_3 and 69% for OIH, but this study shows an extraction that was 61% of that of OIH, indicating a renal extraction efficiency of 53%.

Another requirement for a ^{99m}Tc substitute for hippuran is its ability to assess accurately the percentage contribution by each kidney to the total renal function. A comparison of such values obtained with [^{99m}Tc]MAG_3 and [^{123}I] hippuran in this study shows a highly significant correlation, r = 0.97.

Low protein binding is another requirement. Regarding this aspect for MAG_3 in plasma, an approximate estimation in one patient from a 20-min plasma sample using trichloracetic acid precipitation gave a value of 35%. Taylor et al. (*12*) found 88% but did not specify the technique used. This aspect needs further evaluation.

Another important criterion is the availability of the ^{99m}Tc substitute in the form of a robust kit which is as cheap as DTPA and as easy to prepare. This criterion is not quite met by MAG_3. Although the Mallinckrodt kit is HPLC purified, there is a small amount of lipophilic impurity which is thought to increase with time after preparation so that the [^{99m}Tc]MAG_3 must be used within an hour of the boiling step. There was evidence for some hepatobiliary excretion of MAG_3 during renography and this was confirmed by taking anterior abdominal images at the end of routine study in some

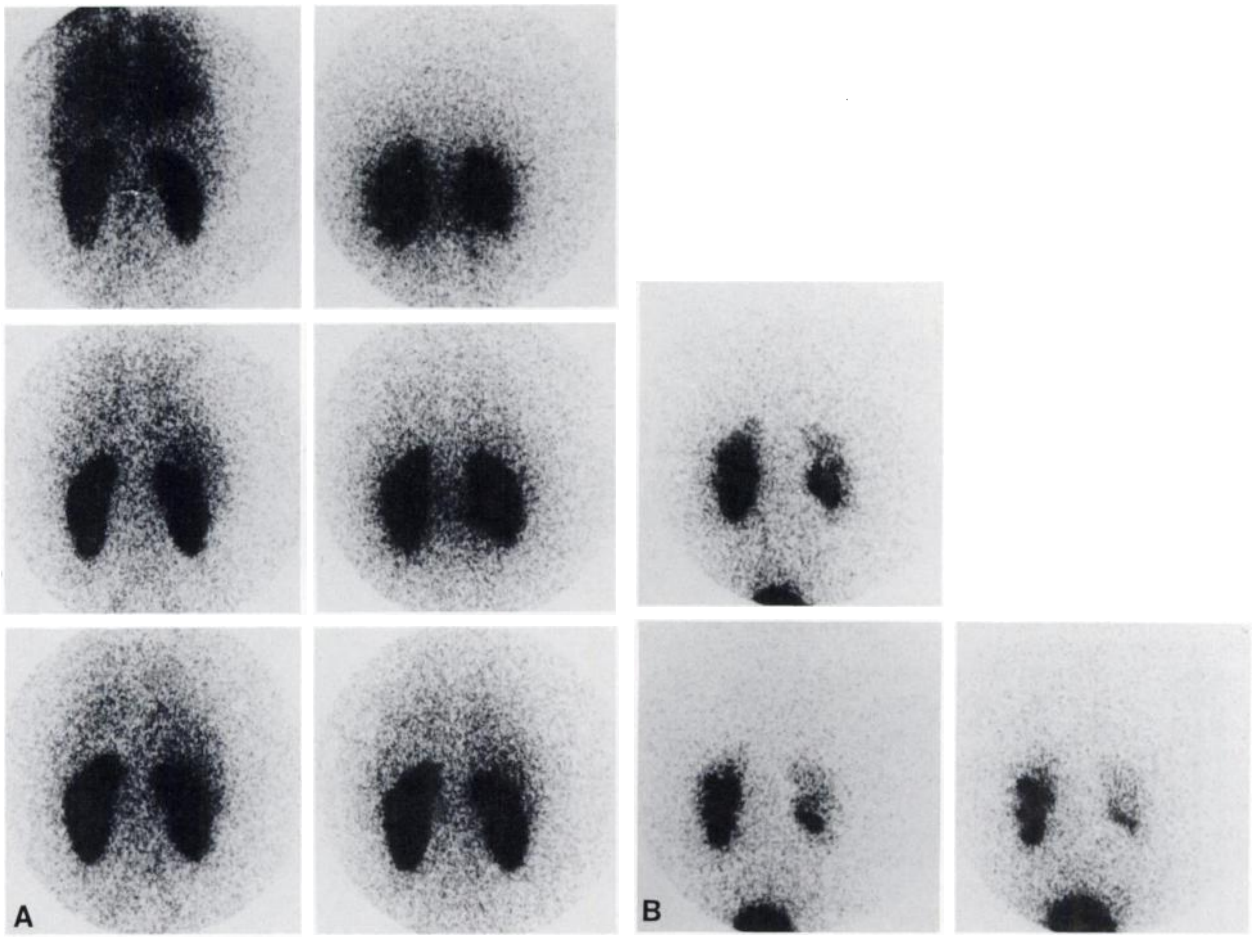

FIGURE 4
[^{123}I]OIH Studies in Case 3. Left nonobstructive hydronephrosis. A: Left-hand images at times 0–30 sec top 30–60 sec middle, 60–90 sec bottom; right-hand images, 90–120 sec bottom, 4.5–5 min middle, 9.5–10 min top. B: Top row images, left 14.5–15 min, right 19.5–20 min damaged-omitted. Bottom row, left 24.5–25 min, right 29.5–30 min. Furosemide given at 18 min.

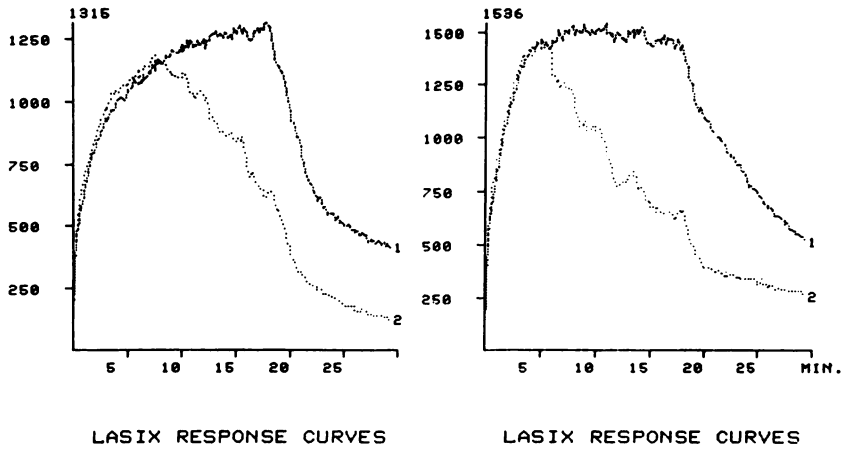

FIGURE 5
Activity-time curves in Case 3. Left non-obstructive hydronephrosis. [^{99m}Tc]MAG_3 on the left, [^{123}I]OIH on the right; vertical scale counts/sec, horizontal scale time in minutes. Furosemide was given at 18 min with a good response on the left side (darker shade, the upper curve).

patients. The degree of liver uptake that is < 4% of the injected dose (Clossens R, personal communication) did not relate to the state of kidney function. This aspect needs further evaluation, but it is thought to be a result of this lipophilic impurity.

The results of the first phase of the study that was to compare the renal clearance of MAG_3 and hippuran shows the clearance values of 58 ml/min to 550 ml/min for MAG_3 and 108 ml/min to 798 ml/min for hippuran with a MAG_3/hipp clearance ratio of 0.61 ± 0.08 (Table 1). The results were quite consistent with the levels of renal function expected on clinical and biochemical assessment of the patients in both cases. The lower clearance values of MAG_3 were found to be

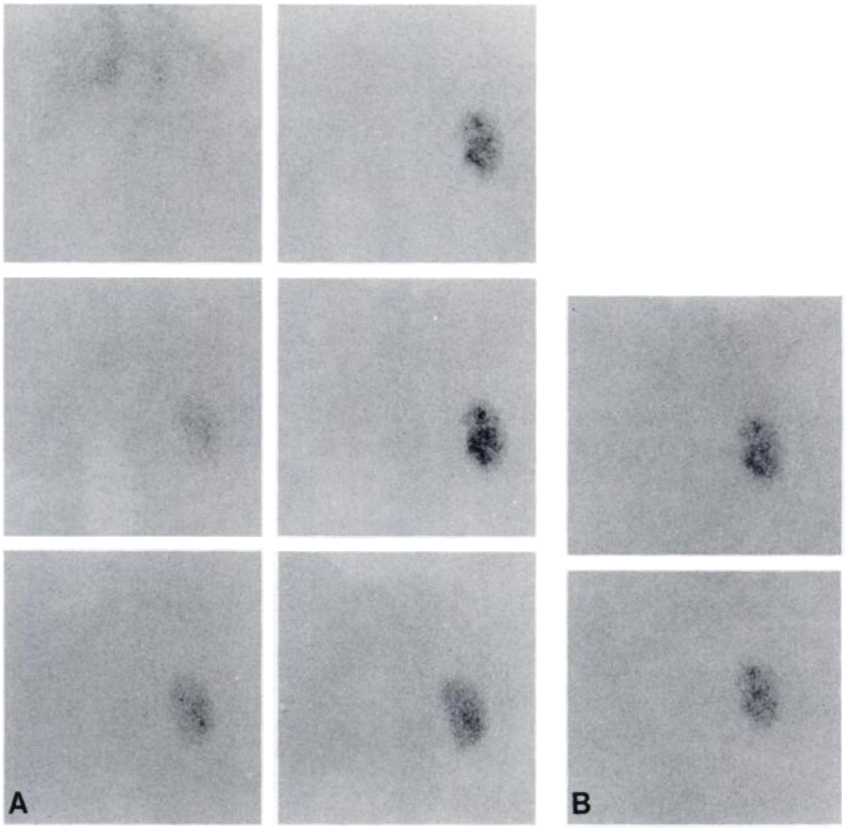

FIGURE 6
[^{99m}Tc]MAG_3 studies in Case 8. Left renovascular disorder. A: Left-hand images at times 0–30 sec top, 30–60 sec middle, 60–90 sec bottom; right-hand images 90–120 sec bottom, 4.5–5 min middle, 9.5–10 min top. B: Top image 14.5–15 min; bottom image 19.5–20 min.

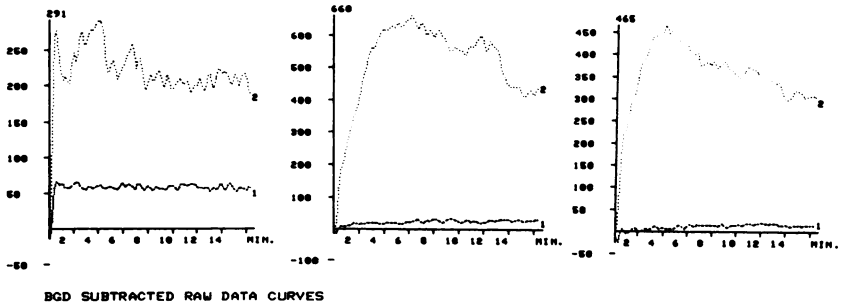

FIGURE 7
Activity-time curves in Case 8. Left renovascular disorder. Left [^{99m}Tc]DTPA; note the high background for the nonfunctioning kidney as compared with [^{99m}Tc]MAG_3 center, and [^{123}I]OIH right.

a result of its significantly lower volume of distribution with MAG_3/hippuran ratio of 0.65 ± 0.08 (Table 1). The rates of clearance were quite similar with a slightly prolonged clearance curve $T_{½}$ for MAG_3 with a MAG_3/hippuran ratio of 1.09 ± 0.12 (Table 1).

This study confirms the finding of Taylor et al. (*12*) that, with simultaneous clearance studies the volume of distribution of [^{99m}Tc]MAG_3 is smaller than that of [^{131}I]OIH. The lower volume of distribution of MAG_3 may reflect lower red cell uptake and stronger protein binding than that of hippuran. It may be also a result of slower diffusion of MAG_3 out of the plasma due to its larger molecular size than hippuran. The volumes of distribution were not measured in the Phase II serial clinical studies. The results of the second phase study in a range of clinical cases showed that the analog images obtained with [^{99m}Tc]MAG_3 were quite similar in quality and information furnished when compared with images obtained with [^{123}I]hippuran in the same patients. The results interpreted with MAG_3 were similar to those with hippuran and were consistent with the clinical condition. In spite of administering four times more [^{99m}Tc]DTPA than the other two agents, the quality of the [^{99m}Tc]DTPA images was inferior.

The more noisy activity-time curve and falsely high activity-time curve in the presence of very low renal function in the [^{99m}Tc]DTPA study in Case 8 is contrasted with the similar curves of [^{99m}Tc]MAG_3 and [^{123}I]OIH in Figure 7.

The success of [^{99m}Tc]MAG_3 in reflecting the findings with [^{123}I]OIH and in bettering the findings with [^{99m}Tc]DTPA have lead to the initiation of a Phase III study of its routine use, replacing [^{99m}Tc]DTPA, for renal evaluation in nephro-urological and hypertensive patients.

It is concluded that [^{99m}Tc]MAG_3 has some advantages over [^{99m}Tc]DTPA and that [^{99m}Tc]MAG_3 is a suitable replacement for [^{123}I]hippuran in routine renal

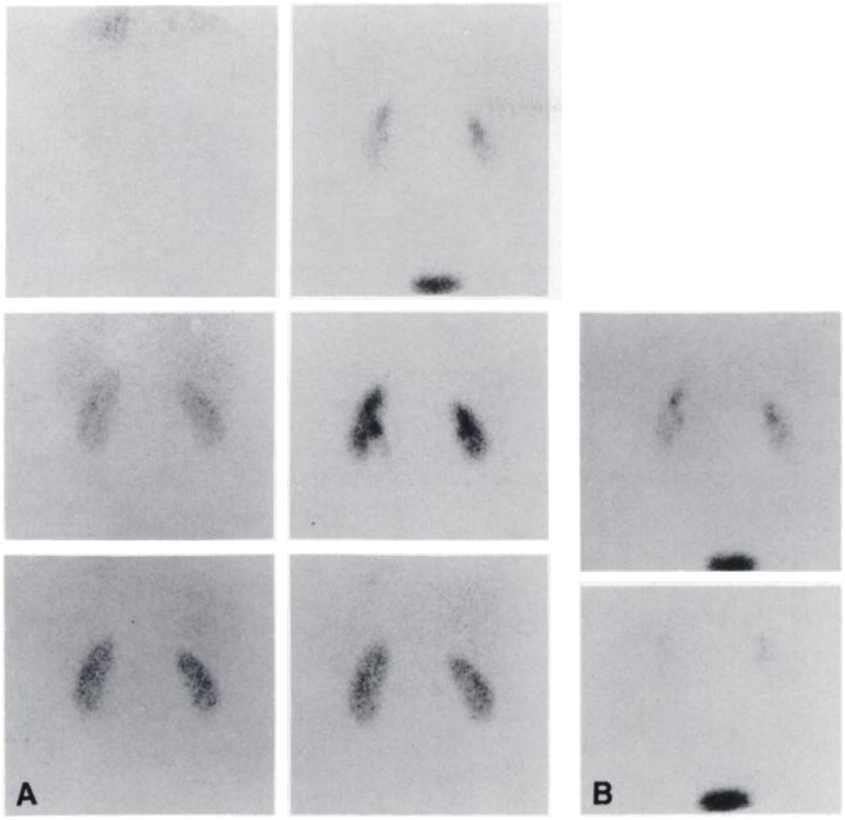

FIGURE 8
[^{99m}Tc]MAG_3 studies in Case 9. A normal result. A: Left-hand images at times 0–30 sec top, 30–60 sec middle, 60–90 sec bottom; right-hand images 90–120 sec bottom, 4.5–5 min middle, 9.5–10 min top. B: Top image 14.5–15 min; bottom image 19.5–20 min.

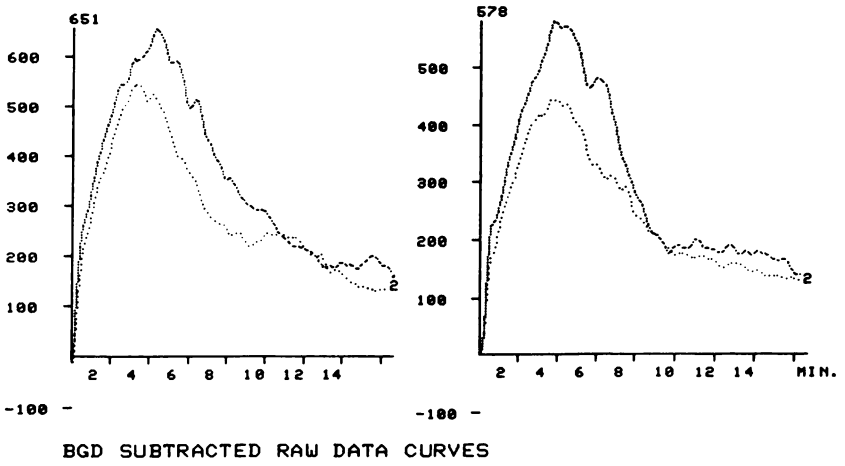

FIGURE 9
Activity-time curves in Case 9. A normal result. Left [^{99m}Tc]MAG_3, right [^{123}I]OIH; vertical scale counts/sec, horizontal scale time in min.

imaging, relative function, and transit time studies but not for the accurate estimation of the renal plasma flow.

NOTES

* Mallinckrodt Diagnostica, Holland.
† Amersham International Ltd., Buckinghamshire, UK.

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ADDENDUM

Under Phase III an additional 80 patients with a variety of renal disorders and levels of renal function including renal transplants, have been studied with 2.5 mCi (92.5 MBq) [^{99m}Tc]MAG_3 in response to routine requests for renal radionuclide evaluation. No adverse reactions have been seen. Excellent qualitative and quantitative data have been obtained with the agent and, in two patients, kidneys were visualized

which could not be demonstrated using 10 mCi (370 MBq) [^{99m}Tc]DTPA. Protein binding of [^{99m}Tc]MAG_3 using a filtration technique has been shown to be 78%.

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