A Comparative Study of Renal Scintigraphy and Clearance with Technetium-99m-MAG_3 and Iodine-123-Hippurate in Patients with Renal Disorders

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The aim of this study was to compare kit prepared technetium-99m-mercaptoacetyltriglycine (^{99m}Tc-MAG_3) with our routine radiopharmaceutical, iodine-123-hippurate our routine radiopharmaceutical, iodine-123-hippurate ([^{123}I]OIH) for renal dynamic scintigraphy. Seventeen patients with different nephrologic disorders or hypertension were first studied with OIH and then reinvestigated with MAG_3 2–8 days later. Renal MAG_3 gamma camera images were almost identical with those of OIH except for higher ($p < 0.01$) liver-to-background ratios at 20 min postinjection, irrespective of kidney function. Urinary peristalsis was visible longer and more clearly in the MAG_3 studies. MAG_3 and OIH renograms showed identical relative kidney uptake ($r = 0.99$), but elimination of MAG_3 from the kidneys was slower ($p < 0.01$). The plasma clearance of MAG_3 was lower than that of OIH, but correlated ($r = 0.92$) significantly. The plasma distribution volume and content in blood cells was lower ($p < 0.01$), but the binding of MAG_3 to plasma proteins was higher, 90%, as compared with 74% for OIH, $p < 0.01$. Urinary excretion expressed as a percent of the given dose 60 min after injection was the same for the two substances. Thus, there are some significant differences in the renal handling, plasma distribution, and cell penetration between MAG_3 and [^{123}I]OIH. MAG_3, however, seems to have particular qualifications as a radionuclide for dynamic renal scintigraphy, especially in patients who require acute investigations or in those with low renal function.

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Recently a new radiopharmaceutical for renal dynamic scintigraphy, technetium-99m-mercaptoacetyltriglycine (^{99m}Tc-MAG_3) has been introduced (*1,2*), which combines the advantage of high renal extraction with a proper energy emission for gamma camera imaging. Animal experiments (*1,3–6*) outlined the excretion characteristics of MAG_3 in comparison with iodine-131-hippurate (*1,4–6*), chromium-51-EDTA, iodine-125-hippurate, and iodine-123-hippurate ([^{123}I] OIH) (*3*), concluding that MAG_3 may be a suitable replacement for hippurate. Clinical trials of MAG_3 at different laboratories in comparison with ^{131}I-hippurate (*2,7–11*), ^{123}I-hippurate (*12*), and ^{99m}TC-DTPA (*13*) have been reported. All authors concluded that ^{99m}Tc-MAG_3 is an efficacious radiopharmaceutical for renal radionuclide studies and a suitable replacement for hippurate as no side effects have hitherto been reported. The present clinical trial was performed to compare MAG_3 with OIH as a renal imaging agent with excellent imaging qualifications, a clearance corresponding to the effective renal plasma flow (ERPF), and a low irradiation dose to the patient. We also wanted to study whether the observation in rats of a significant extrarenal excretion to the bile (*3*) is present in patients. Furthermore, we studied the clearance of MAG_3 in comparison to hippurate because of the debate in literature about the excretion characteristics of MAG_3.

METHODS

Patients

Patients in this study were referred for evaluation of different nephrologic disorders (two for renal cysts, two for pyelonephritis, two for renal dysplasia, one for examination after ureteral surgery, one for renal stone, one for acute renal failure, one for chronic renal insufficiency, and nine for hypertension). All were first investigated with routine ^{123}I-hippuran gamma camera renography. After information of the aim and the procedure of this study was presented, the patients gave their consent to participate in an additional renography with MAG_3 two to eight days later. The study was approved by the ethical committee of Karolinska Institute and the regional isotope-committee.

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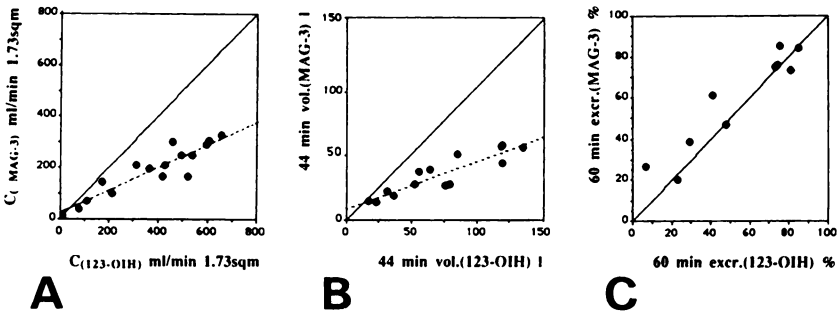

FIGURE 1
Correlation of clearance (A), volume of distribution (B), and of the percent excretion 60 min postinjection (C) between [^{123}I]OIH (abscissa) and MAG_3 (ordinate). Solid lines are the lines of identity, broken lines the regression lines. See text for statistical calculations.

Radionuclides

For the first study, 1 mCi (37 MBq) of [^{123}I]OIH (RadioEIR-isotopenservice, Würenlingen, Switzerland) was used, and for the second study 2 mCi (70 MBq) ^{99m}Tc-mercaptoacetyltriglycine (MAG_3, Mallinckrodt, Petten, Netherlands), which was prepared 60 min before injection by a labeling kit (*14*). To the supplied MAG_3 powder in sealed glass vials, 4 ml 0.9% NaCl solution was added containing ~150 MBq $^{99m}TcO_4$, which was freshly eluted from a technetium generator (Tecegen S, Behringwerke, Frankfort, FRG), eluate ≤ 0.2 ml. The vial was heated in a lead-shielded water bath to ~100°C for 10 min and then cooled under running water. The radiochemical purity (> 95%) was performed according to the manufacturer's recommendation (*13*). Two millicuries of MAG_3 (70 MBq), ~2 ml, were injected intravenously via a three-way connector to a butterfly line and flushed with saline. This MAG_3 preparation was bound at 90% to plasma proteins as measured by a centrifugation filtration technique (Amicon, Centrifree, MA). The corresponding value for our [^{123}I]OIH was 74%.

Clearance Studies

For [^{123}I]OIH, plasma clearance was calculated according to Tauxe and Dubovsky (*15*), i.e., a 44-min one-sample "ERPF" method. For ^{99m}Tc-MAG_3 clearance, six venous plasma samples at 5, 10, 20, 44, 60, and 120 min postinjection were taken from the forearm opposite to the injection arm. MAG_3 clearance was calculated from the injected amount divided by the area under the curve of plasma activity versus time. Bi-exponential curve-fit analysis was used for the calculation of that area. In one patient with acute renal failure, we measured the renal clearance (i.e., U · V/P) by sampling urine over 15 hr. Plasma samples in that case were taken before and after the urine collection and averaged.

For calculation of urine excretion, patients were asked to void 60 min postinjection for urine analysis. The excretion

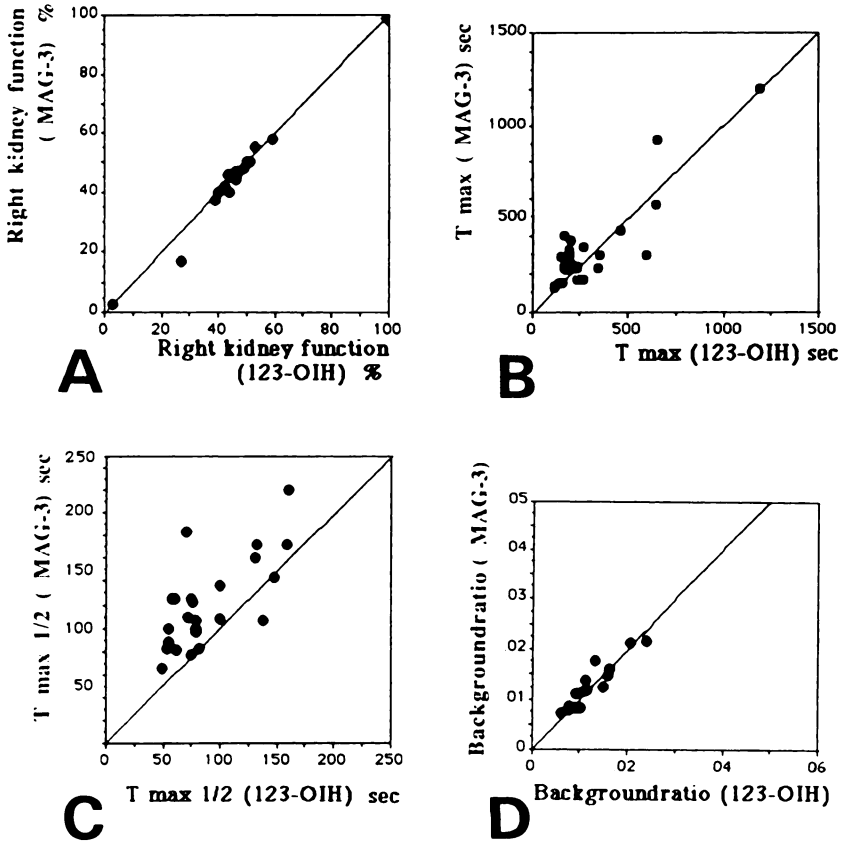

FIGURE 2
Correlation of right kidney function (A), time-to-peak activity ("Tmax") (B), time from peak to 50% activity ("Tmax ½") (C), and ratio between background and renal activity 2–4 min postinjection (D) between [^{123}I]OIH (abscissa) and ^{99m}Tc-MAG_3 (ordinate). Lines of identity are shown. See text for statistics.

was then expressed as percent of the injected amount. For estimation of blood cell content in percent of whole-blood activity, blood was counted using the 44-min samples and corrected for plasma activity and hematocrit.

All counting was done in a well-type counter (Nuclear Data Instruments, Chicago, IL) and corrected for background and weight. Standards of OIH and MAG_3 solutions were prepared at the time of dose preparation and the exact given dose was estimated from standard activity and weight difference of the syringe before and after injection.

Gamma Camera Studies

Patients were studied either supine or seated comfortably in a chair with the gamma camera head placed dorsally covering the region of the kidneys and ureters and part of the bladder. Identical body positions were used for both studies. The patients were normally hydrated with 0.1–0.2 liters of fluid orally just before the study. In case of poor tracer elimination from the kidneys, furosemide, 0.5 mg/kg body weight, was given intravenously 10–15 min after tracer injection. The data were collected in 2.5 sec frame mode by a computer system (Gamma 11) linked to a gamma camera (General Electric, 400 ACT, Milwaukee, IL) to which a high-sensitive, low-energy parallel-hole collimator was fitted. One patient with acute renal failure was, however, studied at bedside in the intensive care unit using a mobile camera (General Electric, 300A) with an internal computer system (Starcam) and the camera head positioned ventrally covering the kidney and ureters. Dynamic pictures were collected for 20 min and additional dorsal pictures, if possible and convenient for the patient, were collected at 60–62 min and 120–122 min post-injection. The data were displayed in a 64 × 64 matrix on a high resolution video monitor.

Regions of interest (ROIs) were set over both kidneys using the 1–3-min postinjection data and over the semilunar background surrounding the individual kidneys. Additional ROIs (4 × 4 pixel) were set over the liver, spleen, and abdominal aorta. From the kidney regions, renogram curves were corrected for kidney depth, and individual semilunar backgrounds of relative renal function (i.e., uptake 60–120 sec postinjection) were calculated. Kidney depth was measured using ultrasound after the first study. The time-to-peak activity (Tmax) was measured and tracer elimination from the kidneys was calculated as the ratio of activity 10 min after peak and peak activity. Also, the time from Tmax to 50% of the activity at Tmax was calculated (Tmax ½) as an index of elimination.

Liver and spleen uptake was determined as the ratio of activity per pixel of liver or spleen region (see above) at 2–4 min, 18–20 min, 60–62 min, or 120–122 min postinjection to the activity per pixel of the background region (aorta).

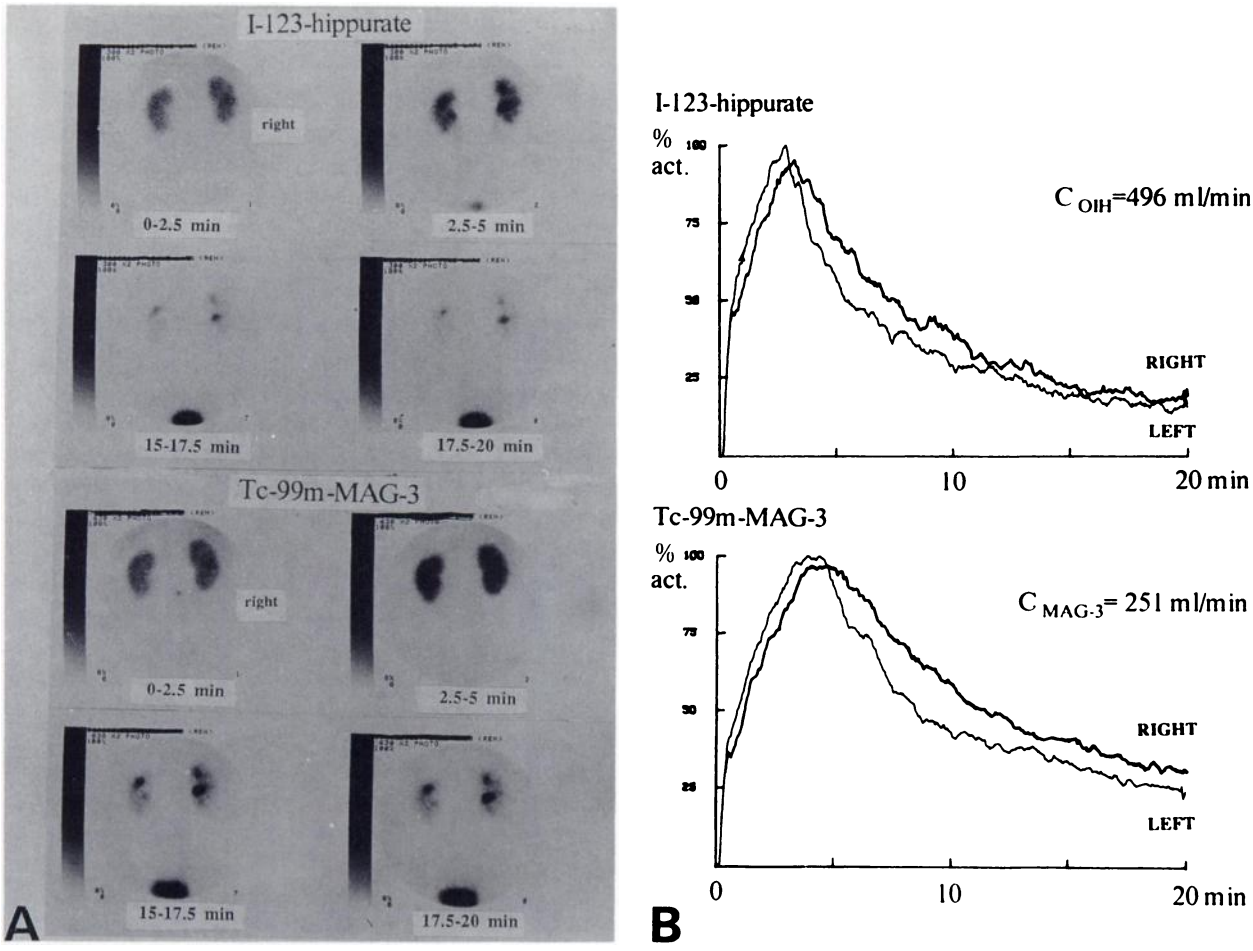

FIGURE 3
(A) Images and (B) renograms of a patient referred for investigation of hypertension. Both studies with [^{123}I]OIH (upper panels) and with MAG_3 (lower panels) show normal pattern, substantially identical. C_{OIH} and C_{MAG3} give plasma clearance values.

Background activity was measured as the ratio of 2–4 min activity of aorta background divided by the sum of the right and left renal activity at the same time.

Ureteral peristalsis was studied by two different approaches. The first consisted in displaying the images on the screen in a dynamic "cine-mode" to assess the peristaltic movements visually. The second method consisted in displaying them in a condensed form as a time-space matrix described by Müller-Schauenburg (*16*) using a special software for the Gamma 11 computer. The steps for matrix generation are:

1. ROI series covering the ureter, the first being the renal pelvis.
2. Corresponding ROI curve series.
3. Background subtraction for each segment in each curve (subtracting either the average or the minimum).
4. The inscription of the subtracted data into a 64 × 64 matrix [y–line = ROI number (i.e., "space", x–row = frame number; i.e., "time").]
5. Displaying the matrix with the upper threshold set to ~20% of the maximum. Ortho-grade peristaltic contractions of the ureter appear as oblique lines in this time-space matrix during tracer elimination from the kidney, i.e., after Tmax on the renogram, normally 1–3/min.

Statistical Analysis

Analysis was performed using the Student's paired t-test or conventional regression analysis to give the correlation coefficient, r. Two-tailed analysis, $p < 0.01$, was viewed as significant. Mean values and s.e.m. are given.

RESULTS

Clearance Studies

None of the patients complained of any side effects from MAG_3. Figure 1 shows the clearance studies data. MAG_3 clearance was significantly lower ($p < 0.001$) than that of OIH (Fig. 1A) but correlated well ($y = 26.134 + 0.4409x$, $r = 0.92$, $p < 0.001$). The distribution volume of the 44-min postinjection of MAG_3 was significantly lower than that for OIH (range 14–59 liters and 17–136 liters, respectively) but correlated well ($y = 9.001 + 0.371x$, $r = 0.82$, $p < 0.001$), see Figure 1B. The excretion rate at 60 min postinjection showed no significant difference between MAG_3 and OIH as seen in Figure 1C where the excretion values are near the line of identity.

The activity in blood cells was measured in eight

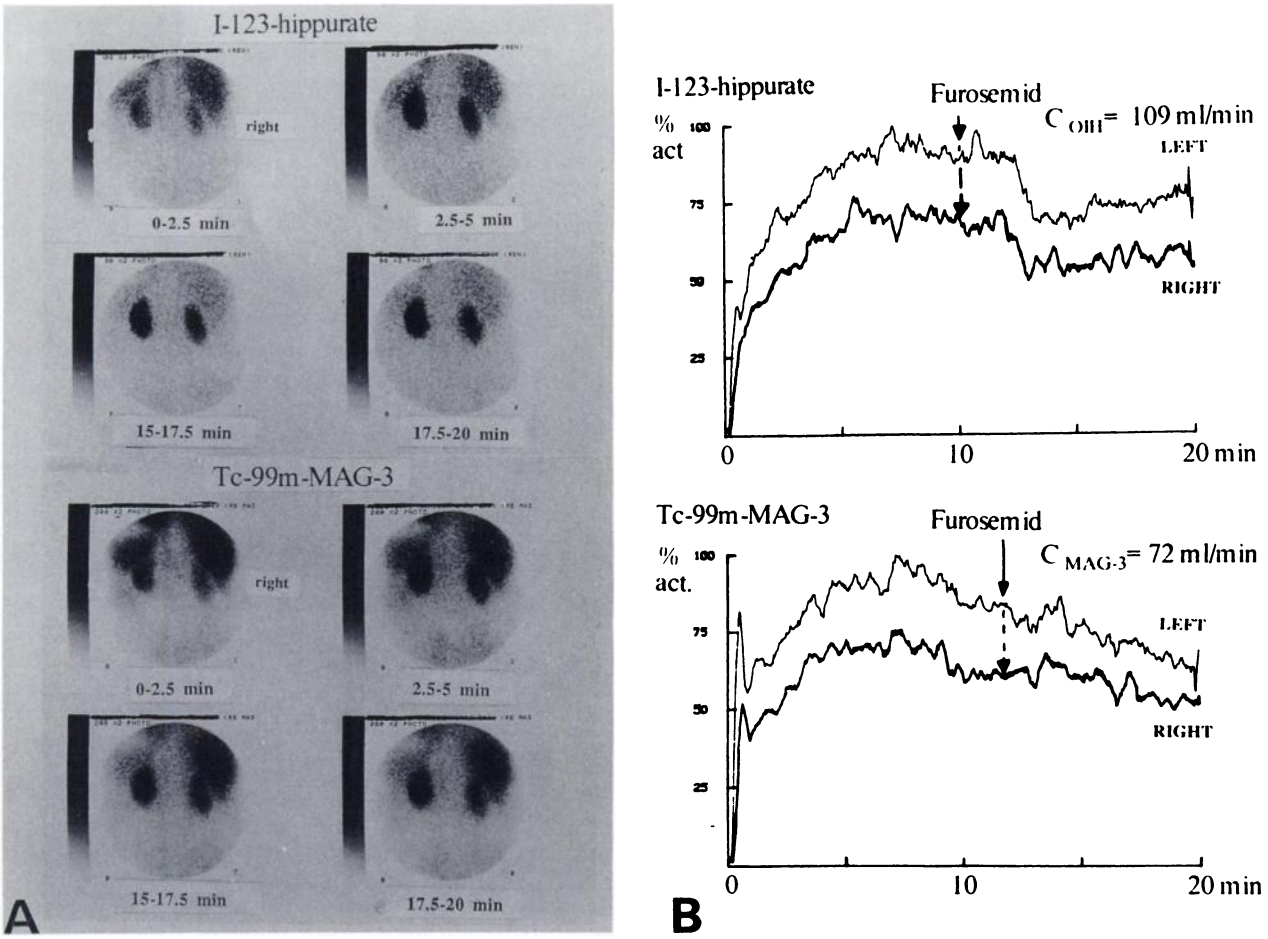

FIGURE 4

(A) Images and (B) renograms of a patient referred for evaluation of suspected urinary tract obstruction. The patient suffered from end-stage renal failure due to recurrent urinary tract infection due to an old spinal cord injury. Significant liver uptake can be seen, particularly in the MAG_3 study (lower panel). Obstruction is excluded by the fact that injection of furosemide shows improved the elimination of the tracers. C_{OIH} and C_{MAG3} give plasma clearance values.

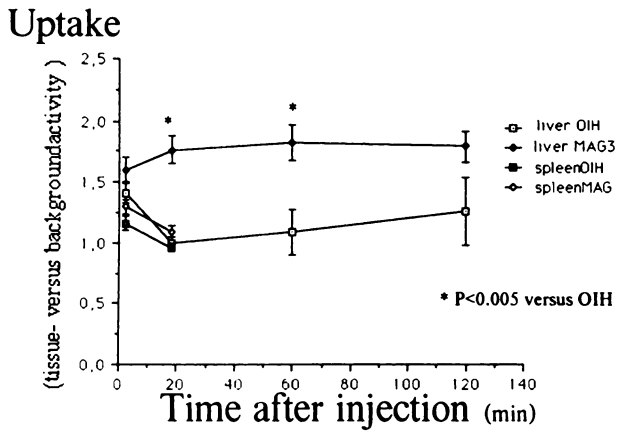

FIGURE 5
Uptake of [^{123}I]OIH and MAG_3 during the time after injection in liver and spleen. Both at 20 and 60 min postinjection, the MAG_3 liver activity is significantly higher than 2–4 min postinjection compared to [^{123}I]OIH. For [^{123}I]OIH and MAG_3, there is a decrease in spleen activity with time, excluding specific uptake.

patients. For MAG_3, it was 7.4% ± 1% of the whole-blood activity as compared to 26.9% ± 3.5% for OIH ($p < 0.01$).

Gamma Camera Studies

Figure 2 shows analytic data of the acquired gamma camera studies. Both calculations of right kidney separate function (Fig. 2A), time-to-peak on renogram (Fig. 2B), and background ratio (Fig. 2D) were not significantly different between MAG_3 and OIH. Elimination of the tracer as measured by Tmax½ was slower in MAG_3 than in OIH, ($p < 0.001$), seen as values above the line of identity in Figure 2C.

Figures 3, 4, and 7 show three examples from different patients. The images obtained with MAG_3 or OIH looked quite similar. In Figure 3, a patient with hypertension shows normal images, renograms, and clearances for both substances. Figure 4, a study of a patient with end-stage renal failure due to recurrent infections after spinal cord injury 15 yr earlier, demonstrates considerable liver uptake of both OIH and MAG_3, but particularly MAG_3. Figure 5 gives the mean values ± s.e.m. of spleen and liver uptake versus time in all patients and demonstrates a specific MAG_3 liver uptake, ~1.5–2.0 times background at 20–120 min postinjection which was not the case for OIH. This uptake was not correlated to kidney function (Fig. 6).

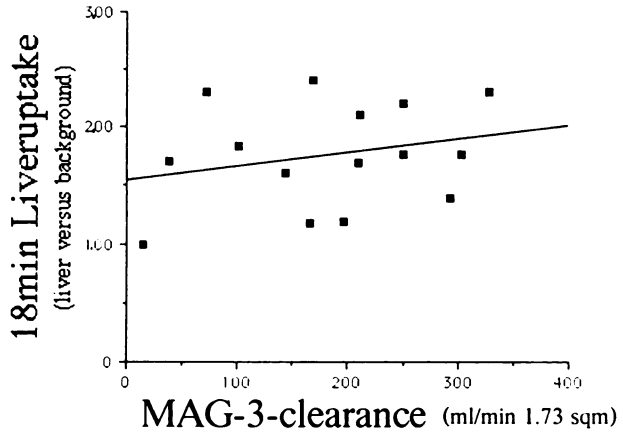

FIGURE 6
Absence of linear correlation ($r = 0.25$) between the renal function, i.e., MAG_3 clearance (abscissa) and the 18–20-min liver uptake of MAG_3 (ordinate).

Urinary peristalsis was visualized in patients with tracer elimination from the kidney to the bladder on screen in the "cine-mode" as well in the condensed form as a time-space matrix (*16*). In most patients, urinary peristalsis was visible more clearly using MAG_3 than OIH, as demonstrated in Figure 7. This patient had earlier pyelonephritis with very low uptake function in the right kidney. The peristalsis of the left ureter is visualized more clearly by MAG_3 than by OIH (compare Fig. 7B lower panel, row a–f corresponding to 5–20 min postinjection for MAG_3, with Fig. 7B upper panel, row a–b corresponding to 2.5–7.5 min for OIH).

DISCUSSION

The present study sought to investigate the clinical value of a new radiopharmaceutical, MAG_3, recently introduced for renal studies (*1,2*) in patients with different degrees of renal function impairment with ERPF varying between 10 and 654 ml/min 1.73 sqm. We used OIH as reference substance for evaluation since MAG_3 has been recommended as a substitute for hippurate. In the first reports, no clinically significant differences were found (*9,10*) besides the observation that MAG_3 clearance was found to be lower than that for hippurate. Some authors recommend the use of a simple correction factor to obtain a value equal to the hippurate clearance, i.e., the ERPF (*17*), whereas others found MAG_3 clearance not suitable for renal plasma flow measurements (*9,18*). In both the present study and others (*3,9,12,13*), there is evidence for extrarenal clearance of MAG_3. However, the exact amount of such an eventual extra renal clearance has not been measured, since it demands both plasma renal clearance measurements simultaneously—which has been done neither in the present study nor in other studies. Thus, the use of a simple correction factor of MAG_3 plasma clearance to obtain renal plasma flow may be incorrect for that reason and also because of estimating errors (*7,9,18*).

Data from animal studies suggest that MAG_3 and hippurate are secreted by the same transport system and are competitively inhibited by probenecid (*2,19*) and PAH (*20*). The lower total renal clearance of MAG_3 is partly a result of lower glomerular filtration as demonstrated by glomerular micropuncture (*21*) due to higher protein binding. Also, a lower renal secretory

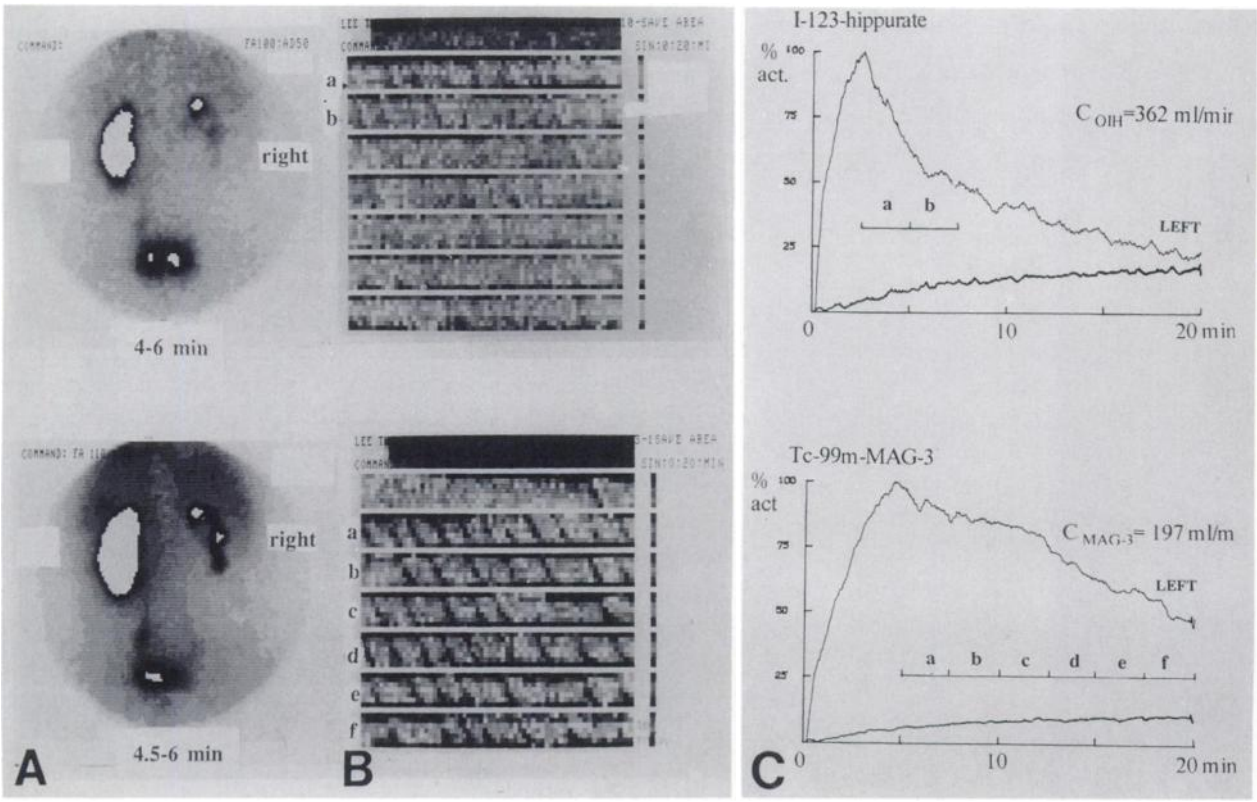

FIGURE 7

(A) Images, (B) time-space matrix, and (C) renograms of a patient with earlier pyelonephritis referred for evaluation of right kidney separate function, which is 3% in both the ^{123}I study (upper panels) and the MAG_3 study (lower panels). Activity lines in the time-space-matrix (B) indicate peristaltic contractions of the left ureter in both studies, which is more clearly seen with MAG_3 (see rows a–f corresponding to 5–20 min postinjection, lower panel) than with [^{123}I]OIH (see rows a and b, i.e., 2.5–7.5 min postinjection, upper panel). Also, elimination of the tracer is slower for MAG_3.

transport capacity for MAG_3 (*5,20,21*) contributes to this difference. Thus, since more than tubular secretion rate determines the MAG_3 clearance, it may not be appropriate to use it for measuring renal tubular excretion rates only, as recommended by Brandau et al. (*20*), especially since we do not know how the different factors are abolished.

Some authors characterize the renal handling of MAG_3 by measuring the excretion rate, i.e., the amount of injected activity in the urine at a certain time postinjection or by whole-blood clearance. Whole-blood clearance for MAG_3 was found to be the same or even higher (*2,4*) than that for hippurate. However, whole-blood clearance is determined both by the penetration process of the tracer into and from the blood cells and by the clearance of the tracer by the kidney. Calculation of renal clearance according to its definition by Smith, i.e., the amount of plasma which is cleared per unit of time, revealed, on the other hand, that MAG_3 clearance is ~50% that of hippurate. This is in good agreement with earlier studies (*3,4,7,9,10,13,18,20*). The excretion rate is also influenced by other factors like volume distribution and the time course of exchange between distribution volume and transport process of excretion. The excretion rate in the present study and in the literature was not significantly different for MAG_3 and OIH, which is a result of a low renal clearance and low distribution volume for MAG_3 and a high renal clearance and high distribution volume for OIH. Higher plasma protein binding and less penetration of MAG_3 into cells as found in the present study and in earlier rat experiments by ourselves and others (*10*) are factors contributing to the lower distribution volume of MAG_3. Russell et al. (*10*) demonstrated no penetration of MAG_3 into blood cells using the American kit of MAG_3, whereas we found some percentage within the cells using the European kit. A technical error, caused by not taking into account the activity in the plasma trapped between the cells using routine blood centrifugation in our case, may be one explanation for this difference. A very low distribution volume could be advantageous for perfusion studies in that MAG_3 gives higher plasma activity in relation to the injected amount than OIH. The high spleen-liver activity of MAG_3 at 2–4 min postinjection may be due to a high blood supply (see Fig. 5). However, in the present study we were unable to investigate perfusion properly since our dosage of MAG_3 and OIH was too low. Transplanted kidneys with abdominal views and a higher dosage may be more suitable for that purpose.

The relative renal uptake was found to be similar for OIH and MAG_3 in accordance with earlier reports (*2, 7,8,9,13*), as was the time-to-maximum peak activity on the renogram since both substances are predominantly excreted by tubular secretion. The elimination of the tracer from the kidneys was, however, in the present study slower for MAG_3 than for OIH. This was evidently not explained by different urine flow rates. The lower renal clearance of MAG_3 might have been of importance.

Slow elimination together with high target-to-background ratios and the use of a high dose of MAG_3 may be factors which made it possible to visualize the ureters and their peristalsis. In most patients, ureteral peristalsis in the time-space matrix (*16*) could be demonstrated and followed more clearly with MAG_3 than with OIH (Fig. 7). Another difference in imaging quality was the higher liver uptake of MAG_3, which has been observed earlier in rat experiments (*3*) and described in patients (*9,7,13*). Brandau et al. (*20*) did not observe liver uptake using HPLC-purified MAG_3 in humans. Thus, kit-prepared MAG_3 seems to differ in this respect, although bile excretion of HPLC-purified MAG_3 has been demonstrated to do so (*3*), and other possible factors may be involved. Since the specific liver uptake is slow and seen only in late pictures and not more than twice in background activity, it does not jeopardize reliable calculation of separate function of the right kidney and is, therefore, of limited clinical significance.

In summary, there are some significant differences in the renal handling, the plasma distribution, and the cell penetration of MAG_3 and OIH. MAG_3, however, seems to have particular qualifications as a radionuclide for dynamic renal scintigraphy since it is easily available by kit for labeling with ^{99m}Tc and has a higher renal excretion rate than a glomerular marker like DTPA. Despite the lower clearance of MAG_3 in comparison to hippurate, its lesser cell penetration and its higher target-to-background ratio results in renal dynamic scintigrams of high quality. Thus, from a clinical point of view, MAG_3 has advantages over other radiopharmaceuticals especially in patients with low renal function who require acute investigations.

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