Clinical Evaluation of Technetium-99m-L,L-Ethylenedicysteine in Patients with Chronic Renal Failure

Elizabeth M. Prvulovich, Jamshed B. Bomanji, Wendy A. Waddington, Ponnuthurai Rudrasingham, Alfons M. Verbruggen and Peter J. Ell

Institute of Nuclear Medicine, University College London Medical School, London, United Kingdom; Laboratory of Radiopharmaceutical Chemistry, Catholic University, Leuven, Belgium

Technetium-99m-L,L-ethylenedicysteine (^{99m}Tc-L,L-EC), a new renal radiopharmaceutical, has been shown to have similar excretion characteristics but a higher plasma clearance than ^{99m}Tc-mercaptoacetyltriglycine (^{99m}Tc-MAG3) in normal volunteers and patients with obstructive nephropathy. This study evaluated ^{99m}Tc-L,L-EC in patients with chronic renal failure. **Methods:** The clearance of ^{99m}Tc-L,L,-EC was compared with that of ^{125}I-hippuran in 26 patients with varying degrees of chronic renal impairment (serum creatinine 168-1163 μmol/liter). All 26 patients also were imaged with ^{99m}Tc-L,L-EC (70–80 MBq). Fifteen patients had further imaging with ^{99m}Tc-MAG3 (100 MBq) the following day. **Results:** A subjective analysis of the ^{99m}Tc-L,L-EC images revealed that all were of acceptable quality regardless of creatinine level. In the 15 patients who were imaged with both ^{99m}Tc-L,L-EC and ^{99m}Tc-MAG3, general image quality and target-to-background ratios were similar. Time-activity curves and mean parenchymal transit times obtained with the two agents were almost identical. Plasma clearance values (mean ± s.d.) of ^{99m}Tc-L,L-EC and ^{125}I-hippuran were 81 ± 68 ml/min and 114 ± 104 ml/min, respectively. Mean ^{99m}Tc-L,L-EC clearance was 71% of the mean ^{125}I-hippuran value. **Conclusion:** Technetium-99m-L,L-EC provides equally high-quality images to ^{99m}Tc-MAG3 in patients with chronic renal failure. Technetium-99m-L,L-EC clearance more closely resembles that of hippuran than does ^{99m}Tc-MAG3 clearance. These features together with its ease of preparation make ^{99m}Tc-L,L-EC an attractive alternative to ^{99m}Tc-MAG3 in patients with chronic renal failure.

Key Words: chronic renal failure; technetium-99m-L, L-EC

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Many patients with chronic renal failure have renal scintigraphy to detect treatable conditions, such as obstruction. For many years radioiodinated ortho-iodohippurate (hippuran) was the principal renal radiopharmaceutical used in patients with impaired renal function. The high plasma clearance of radioiodinated hippuran meant this agent could be used to measure effective renal plasma flow (ERPF) while its high plasma extraction (*1,2*) enabled scintigraphy in patients with impaired renal function. Unfortunately, neither ^{131}I nor ^{123}I are optimal labels for this radiopharmaceutical. Iodine-131-hippuran (364-keV gamma rays, physical half-life 8 days) is associated with a high radiation dose particularly when there is impaired renal function and scintigraphic images are of poor quality. Iodine-123-hippuran has good biological and radiation characteristics (159-keV gamma rays, physical half-life 13 hr) but suffers from limited availability and high cost. For these reasons, ^{99m}Tc-MAG3 was developed as a hippuran substitute (*3*).

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For correspondence or reprints contact: Jamshed B. Bomanji, MD, Institute of Nuclear Medicine, University College London Medical School, Mortimer St., London W1N 8AA, United Kingdom.

The high extraction fraction of ^{99m}Tc-MAG3 (*4,5*) means that high-quality images can be obtained in patients with impaired renal function. It has, therefore, replaced hippuran for imaging in most centers. Unfortunately, the plasma clearance of ^{99m}Tc-MAG3 is less than 65% of hippuran clearance (*6,7*) and accurate ERPF estimation is relatively difficult. The need for a boiling step during radiopharmaceutical preparation is another disadvantage. Recently, a new ^{99m}Tc-labeled renal radiopharmaceutical, ^{99m}Tc-L,L-ethylenedicsyteine (^{99m}Tc-L,L-EC), has been developed. Technetium-99m-L,L-EC is the diacid derivative of the brain perfusion agent ^{99m}Tc-ethyl cysteinate dimer (^{99m}Tc-L,L-ECD) and contains an oxotechnetium-glycine sequence that structurally resembles the carbonylglycine side chain of hippuran. In normal volunteers and patients with obstructive nephropathy, ^{99m}Tc-L,L-EC has similar extraction, excretion and renogram patterns as ^{99m}Tc-MAG3 (*8,9*) and hippuran (*10*) but a lower rate of excretion through the hepatobiliary system (*11*). Importantly, studies also demonstrated that ^{99m}Tc-L,L-EC has a 20% higher plasma clearance (*8,12*) than ^{99m}Tc-MAG3. To date only a handful of patients with chronic renal failure have been evaluated using ^{99m}Tc-L,L-EC. The purpose of this study was to compare ^{99m}Tc-L,L-EC with ^{99m}Tc-MAG3 and ^{125}I-hippuran in patients with chronic renal failure and to determine whether ^{99m}Tc-L,L-EC is a realistic alternative to ^{99m}Tc-MAG3 in this group of patients. Technetium-99m-L,L-EC was compared with ^{125}I-hippuran with respect to plasma clearance and distribution volume using both multiple- and single-sample data, and with ^{99m}Tc-MAG3 with respect to renal imaging.

MATERIALS AND METHODS

Subjects

Twenty-six patients (7 women, 19 men) with chronic renal failure were selected as the study group from among patients referred to our department for radionuclide renography. Patients ranged in age from 21 to 80 yr of age, median age was 60 yr. The etiology of chronic renal failure was quite diverse: common diagnoses included hypertensive, diabetic and reflux nephropathy (Table 1). Two patients had solitary kidneys. Mean serum creatinine was 466 μmol/liter, range 168-1163 μmol/liter. Creatinine clearance values ranged from 1–63 ml/min, mean value 12 ml/min. The study was approved by the Hospitals Clinical Trials Committee and the Administration of Radioactive Substances Advisory Committee (ARSAC). Patients under 18 yr of age and pregnant women were excluded.

The clearance of ^{99m}Tc-L,L-EC was compared with that of ^{125}I-hippuran in all patients. All 26 patients also underwent imaging with ^{99m}Tc^{m}-L,L-EC. Fifteen patients underwent further imaging with ^{99m}Tc-MAG3 the following day.

TABLE 1
Patient Data

Clinical diagnosis	No. of patients	Age range (yr)	Creatinine clearance (ml/min)	^{99m}Tc-L,L-EC clearance (ml/min/1.73^2)
Diabetes	4	39–61	2–23 (mean 14)	39–87 (mean 56)
Hypertension	6	21–80	1–8 (mean 3)	10–216 (mean 77)
Carcinoma	5	53–70	1–63 (mean 14)	38–284 (mean 121)
Reflux	3	21–46	2–19 (mean 12)	41–87 (mean 68)
Others	8	43–80	2–25 (mean 12)	40–148 (mean 71)

Radiopharmaceutical Preparation

Technetium-99m-L,L-EC was prepared by reconstituting a two-vial labeling kit. Vial A contained 0.5 mg of L,L-EC, 10 mg of $Na_2HPO_4.2H_20$, 45 mg of $Na_3PO_40.12H_20$ and 0.1 mg of $SnCl_2.2H_20$ in lyophilized form. Vial B contained a 0.545-*M* solution of $NaH_2PO_4.2H_2O$ in water for injections. Labeling was performed under aseptic conditions. In a volume not exceeding 5 ml, 1000 MBq of sodium ^{99m}Tc-pertechnetate was added to the vial that contained L,L-EC followed by the addition of 0.25 ml solution of vial B to adjust the pH to 7.5–8.5.

Technetium-99m-MAG3 was prepared from commercial labeling kits according to the manufacturer's instructions. In both preparations free pertechnetate and colloidal ^{99m}Tc were less than 2%, as determined by thin-layer chromatography (*11*).

Iodine-125-hippuran was obtained from commercial sources and was specifically designed for the measurement of ERPF. The amount of activity in the vial was 20 MBq (approximately 0.5 mCi) in 10 ml. Free radioiodine was below 2%, according to the manufacturer's specifications.

Administered Doses

In all 26 patients, 70–80 MBq ^{99m}Tc-L,L-EC and 1–2 MBq ^{125}I-hippuran was given according to ARSAC recommendations. In 15 patients, 80–100 MBq ^{99m}Tc-MAG3 was also given after a 1-day interval to acquire renal images for comparison with ^{99m}Tc-L,L-EC.

Procedure

The patient was placed in a supine position. A large field-of-view gamma camera with a general-purpose collimator was positioned beneath the patient so that both the heart and kidneys were in the field of view. Technetium-99m-L,L-EC was injected as a bolus through a three-way connector into a butterfly line and flushed with 10 ml of saline. Iodine-125-hippuran was injected within a minute of ^{99m}Tc-L,L-EC injection. Technetium-99m-MAG3 was injected in an identical manner to ^{99m}Tc-L,L-EC on a subsequent day.

Renogram Acquisition and Analysis

Renogram acquisition and analysis parameters for ^{99m}Tc-L,L-EC and ^{99m}Tc-MAG3 were similar. Data was acquired for 25 min. The first 40 frames were acquired for 1 sec each followed by 146 frames of 10 sec. A 128 × 128 word-depth matrix was used for acquisition. One-minute pre- and postmicturition static images were also acquired.

The renogram data was reframed into 150 10-sec frames. ROIs were drawn over each whole kidney and the renal pelvis using the 2- to 3-min composite image. To correct for background activity, an ROI was drawn medial to each kidney and for deconvolution analysis an ROI was placed over the left ventricle. From these images, computer-generated time-activity curves were obtained and the relative renal function was derived. Deconvolution analysis with a matrix algorithm method was used to calculate the mean parenchymal transit times (*13*). The scintigraphic images obtained with ^{99m}Tc-L,L-EC and ^{99m}Tc-MAG3 were assessed visually and compared. Images were assessed specifically for tracer distribution and target-to-background ratio as well as general image quality.

Blood Samples for Plasma Clearance

An additional cannula was placed in the contralateral arm to obtain 10-ml blood samples at 2, 15, 30, 44, 60, 120 and 180 min after injection. At the end of the study, the sample tubes were centrifuged to separate the plasma, and 2 ml of plasma were placed in tubes for counting. Standards of ^{99m}Tc-L,L-EC and ^{125}I-hippuran were prepared at the time of dose preparation. Standards and plasma samples were assayed in a calibrated dual-channel counter. Correction was made for physical decay during counting and samples were counted for ^{125}I after decay of ^{99m}Tc activity. Iodine-125-hippuran and ^{99m}Tc-L,L-EC clearances were calculated using the methods of Sapirstein (*14*) and Tauxe (*15*). Sapirstein's method is a two-compartment method requiring a single injection and multiple plasma samples. The total volumes of distribution for ^{99m}Tc-L,L-EC and ^{125}I-hippuran were calculated from this method. Tauxe's method requires a single plasma sample taken 44 min after injection. Clearance values for both methods were normalized to 1.73 m^2 body surface area.

Statistical Analysis

Student's t-test was performed to compare the mean parenchymal transit times obtained in the 15 patients imaged with both ^{99m}Tc-L,L-EC and ^{99m}Tc-MAG3. A $p < 0.05$ was taken as significant. To examine the differences of plasma clearance and volume of distribution of ^{99m}Tc-L,L-EC and ^{125}I-hippuran data, the paired Student's t-test was used. Any $p \leq 0.05$ was regarded as significant. All regression analyses were made for $p \leq 0.05$ (95% confidence intervals).

RESULTS

Renogram Data

Fifteen patients were imaged using both ^{99m}Tc-L,L-EC and ^{99m}Tc-MAG3; 11 patients were imaged using ^{99m}Tc-L,L-EC only.

Subjective analysis of ^{99m}Tc-L,L-EC images revealed that all were of acceptable quality regardless of creatinine level. In the 15 patients who were imaged with both ^{99m}Tc-L,L-EC and ^{99m}Tc-MAG3, general image quality, tracer distribution and target-to-background ratios were similar (Figs. 1, 2). Typically, kidneys were small and concentrated and excreted tracer poorly. Background activity remained high throughout the study. In 3 of 15 (20%) patients improved renal delineation was seen with ^{99m}Tc-L,L-EC as compared with ^{99m}Tc-MAG3.

Time-activity curves obtained with the two agents were almost identical; curves were subject to noise and reflected the poor uptake and low clearance of the tracer. The nature of the time-activity curves meant that time to peak activity and time to half-peak activity could not be meaningfully assessed in all patients.

Mean parenchymal transit times (MPTT) for both ^{99m}Tc-L,L-EC and ^{99m}Tc-MAG3 could be calculated for 10 of 15 patients imaged with both agents. MPTT for ^{99m}Tc-L,L-EC and ^{99m}Tc-MAG3 were similar and ranged from 144 to 458 sec (mean 248 sec) and 122 to 471 sec (mean 279 sec), respectively ($p = 0.3$). In the other studies, poor renal function led to uninterpretable deconvolution data.

There was no difference in the amount or quality of clinical and diagnostic information provided by ^{99m}Tc-L,L-EC and ^{99m}Tc-MAG3 studies at all levels of renal impairment.

Plasma Clearance Data

The difference between the plasma clearance values using multiple samples (Table 2) for ^{99m}Tc-L,L-EC and ^{125}I-hippuran

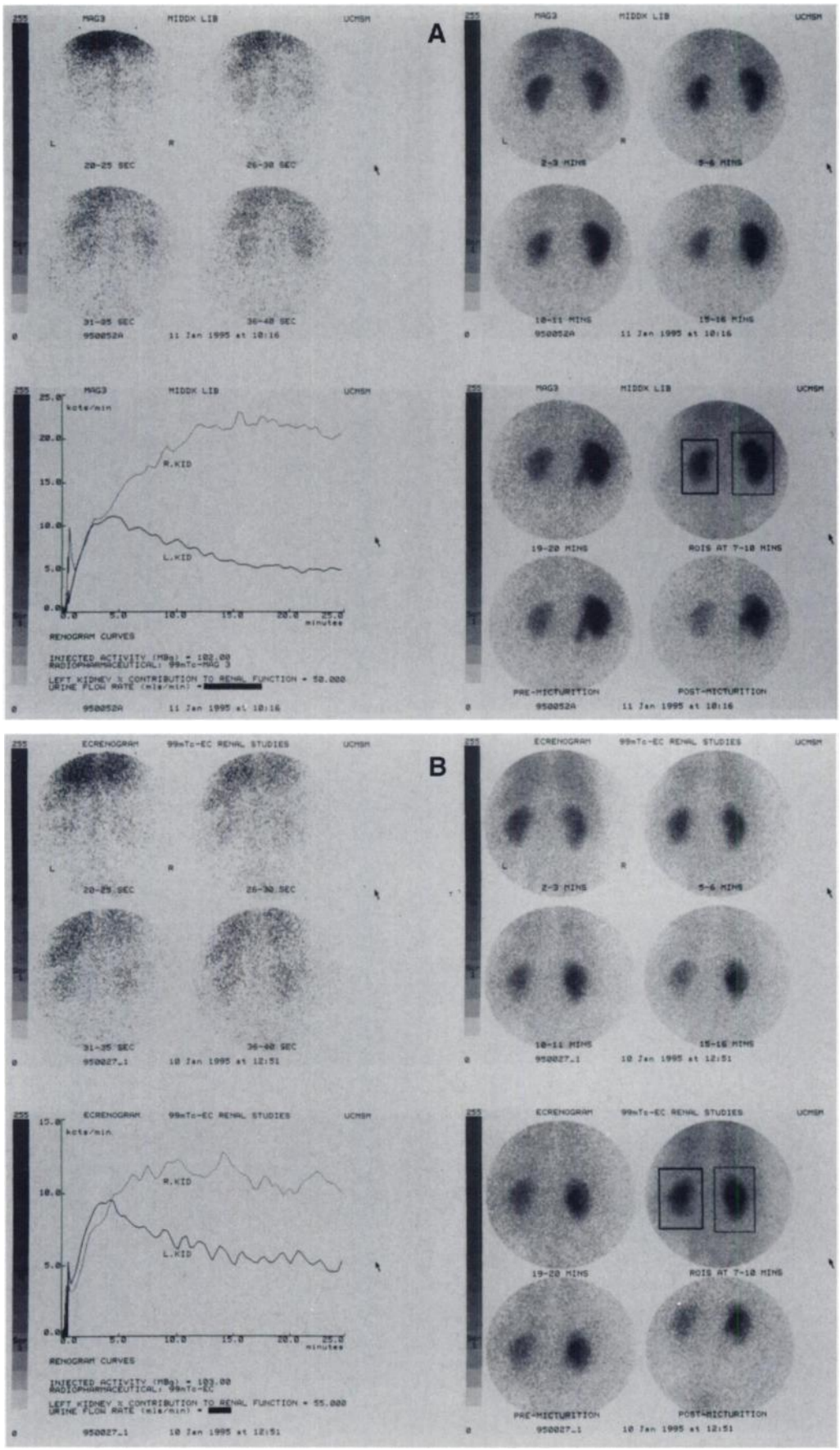

FIGURE 1. Patient with prostate carcinoma and oliguria: creatinine clearance 25 ml/min. On the (A) ^{99m}Tc-MAG3 and (B) ^{99m}Tc-L,L-EC images, the right kidney, in comparison with the left kidney appears larger and with tracer retention within it compared to the left kidney.

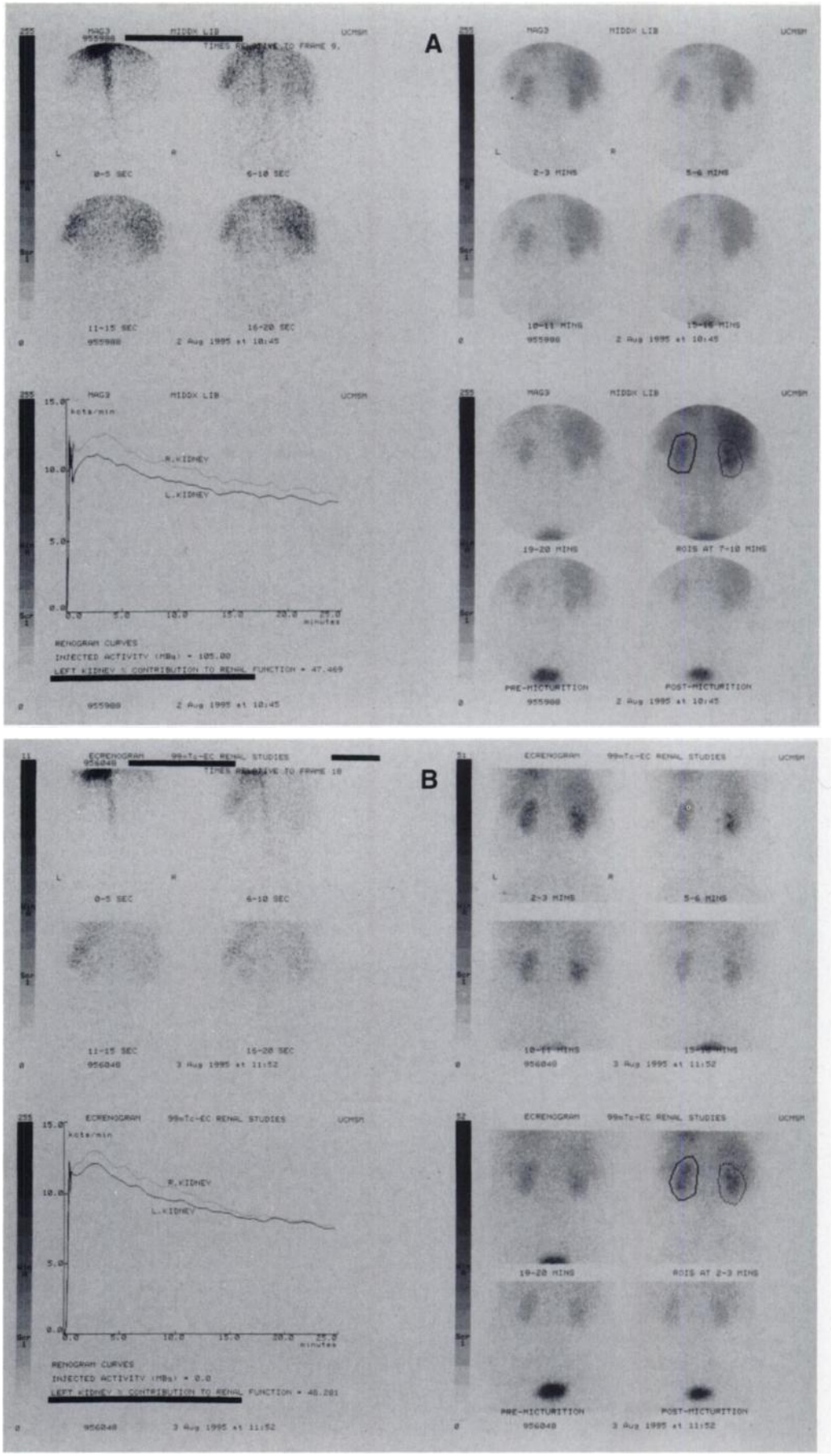

FIGURE 2. Patient with longstanding hypertension: creatinine clearance 8 ml/min. On both the (A) ^{99m}Tc-MAG3 and (B) ^{99m}Tc-L,L-EC images, the kidneys appear small with irregular cortical outlines and there is poor uptake of tracer bilaterally and unremarkable tracer excretion.

TABLE 2
Plasma Clearance and Distribution Volume (mean ± s.d.) Data for Iodine-125-Hippuran and Technetium-99m-L,L-EC

	^{125}I-hippuran	^{99m}Tc-L,L-EC
Total distribution volume (liter)	22.8 ± 10.4	20.4 ± 9.2
Clearance (multiple samples) (ml/min/1.73m^2)	114 ± 104 (range 19–376)	81 ± 68 (range 10–284)
Clearance (single sample) (ml/min/1.73m^2)	131 ± 83 (range 42–327)	103 ± 65 (range 34–259)

was significantly different ($p = 0.0066$). Figure 3 shows the correlation of these values ($r = 0.91$; $p < 0.001$; 95% confidence interval). Taking ^{125}I-hippuran clearance as the reference (100%), mean ^{99m}Tc-L,L-EC (multiple sample) clearance was 71% of the mean ^{125}I-hippuran clearance value.

Total Distribution Volume

Total distribution volume based on plasma values for ^{99m}Tc-L,L-EC was similar to that for ^{125}I-hippuran ($p = 0.06$). Taking the distribution volume of ^{125}I-hippuran as the reference (100%), mean ^{99m}Tc-L,L-EC distribution volume was 89% of the ^{125}I-hippuran distribution volume. Table 2 shows the clearance values and distribution volumes of ^{99m}Tc-L,L-EC and ^{125}I-hippuran.

DISCUSSION

High-quality renograms can be obtained in patients with chronic renal failure with ^{99m}Tc-MAG3, but because its plasma clearance is less than 65% that of hippuran, ERPF measurements are rather meaningless (*6–7*). A ^{99m}Tc-labeled radiotracer with renal excretion characteristics, comparable to those of ^{99m}Tc-MAG3 but with a plasma clearance closer to that of hippuran and allowing direct measurement of ERPF, would be an improvement.

Technetium-99m-L,L-EC has been evaluated in normal volunteers, patients with obstructive nephropathy and renal transplant recipients (*8–10,16*). Similar quality renograms were provided by ^{99m}Tc-L,L-EC and ^{99m}Tc-MAG3 (*8–10*) but ^{99m}Tc-L,L-EC plasma clearance was shown to be 20% higher than that of ^{99m}Tc-MAG3 (*8*).

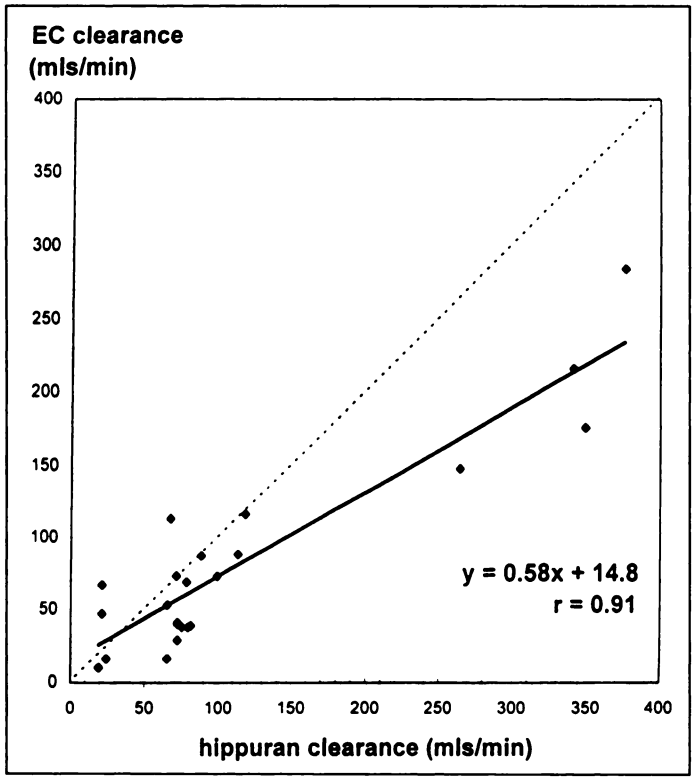

FIGURE 3. Correlation of the simultaneously-determined ^{99m}Tc-L,L-EC with the ^{125}I-hippuran clearance in 23 patients.

Few patients with impaired renal function have been evaluated with ^{99m}Tc-L,L-EC. As studies with ^{99m}Tc-N,N′-bis-(mercaptoacetyl)−2,3-diamino-propanoate (^{99m}Tc$^{-CO_2}$DADS) have revealed, the fact that a renal agent performs well in volunteers is not a guarantee that it will perform well in patients with impaired renal function (*17*).

This study sought to investigate the clinical value of ^{99m}Tc-L,L-EC in patients with varying degrees of renal impairment documented by raised serum creatinine and depressed creatinine clearance values. We used ^{125}I-hippuran and ^{99m}Tc-MAG3 as reference agents.

Our results indicate that ^{99m}Tc-L,L-EC provided images of acceptable quality in all patients regardless of creatinine level and that ^{99m}Tc-L,L-EC and ^{99m}Tc-MAG3 provided similar quality images in these patients.

The clearance values we obtained were quite consistent with the levels of renal function expected on clinical and biochemical assessment. The mean value of ^{99m}Tc-L,L-EC clearance (multiple sample method) in patients with chronic renal failure was 71% of that of hippuran. This value for ^{99m}Tc-L,L-EC clearance relative to hippuran clearance is similar to that previously reported in patients with preserved renal function and mild renal impairment (*8,9,12,18*). Technetium-99m-MAG3 clearance previously has been reported to be less than 65% of that of hippuran (*6,7*). Technetium-99m-L,L-EC would, therefore, appear to have a plasma clearance closer to that of hippuran than ^{99m}Tc-MAG3 even when renal function is severely impaired. In clinical practice, the use of normal clearance values of ^{99m}Tc-L,L-EC coupled with renal scintigraphy could provide useful information about renal function, but not the true ERPF.

The total volume of distribution of ^{99m}Tc-L,L-EC and ^{125}I-hippuran was similar ($p = 0.06$). The volume of distribution of ^{99m}Tc-MAG3 was not calculated in this study, however, it has been shown on many occasions that ^{99m}Tc-MAG3 has a significantly smaller volume of distribution than both hippuran and ^{99m}Tc-L,L-EC (*5,6,12,18*). The higher volume of distribution of ^{99m}Tc-L,L-EC, compared to that of ^{99m}Tc-MAG3, can be attributed both to its lower protein and red blood cell binding. Other authors have shown that 31% of ^{99m}Tc-L,L-EC is protein bound compared with 88% of ^{99m}Tc-MAG3 and 68% of ^{125}I-hippuran (*8*) and that 3% of ^{99m}Tc-L,L-EC is bound to red blood cells compared to 27% of ^{125}I-hippuran (*10*). It is assumed that the higher volume of distribution of ^{99m}Tc-L,L-EC together with the important large fraction filtered by the glomeruli (*19*) contributes mainly to the higher plasma clearance of ^{99m}Tc-L,L-EC.

Previous studies have evaluated ^{99m}Tc-L,L-EC in patients with impaired renal function. Gupta and colleagues evaluated five patients with varying degrees of chronic renal failure using ^{99m}Tc-L,L-EC and ^{99m}Tc-MAG3 (*9*). They reported that images of similar quality were obtained with the two agents. Plasma clearance was not measured in this study. Kabasakal et al. (*12*) studied only three patients with chronic renal failure and conclusions are, therefore, hard to draw from their data.

Our imaging data confirm that high-quality renal images can be acquired in patients with impaired renal function using ^{99m}Tc-L,L-EC. Improved renal delineation with ^{99m}Tc-L,L-EC, compared with ^{99m}Tc-MAG3, was seen in our study. This has previously been reported only in animals and patients with preserved renal function (*8–10,11,18*).

The usefulness of a tracer agent as a routine radiopharmaceutical is determined not only by its in vivo behavior but also by practical aspects such as ease of preparation and stability. In this regard, ^{99m}Tc-L,L-EC is preferable to ^{99m}Tc-MAG3 even though the preparation of both radiopharmaceuticals is a two-step procedure. Technetium-99m-L,L-EC has the convenience of a labeling procedure that can be performed rapidly at room temperature to achieve a preparation of high radiochemical purity that remains stable throughout the day (*11*). By contrast, the preparation of ^{99m}Tc-MAG3 involves a boiling step and stability after this step is limited to between 1 and 4 hr depending on the concentration of the preparation.

CONCLUSION

In our series of patients with chronic renal failure, ^{99m}Tc-L,L-EC compared favorably with ^{99m}Tc-MAG3. Technetium-99m-L,L-EC is an attractive alternative to ^{99m}Tc-MAG3 in patients with impaired renal function. It provides equally high-quality images but has the advantage of enhanced simplicity of preparation. Furthermore, compared to ^{99m}Tc-MAG3, it more closely resembles hippuran.

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Evidence of Accelerated Gastric Emptying in Longstanding Diabetic Patients After Ingestion of a Semisolid Meal

Rainer W. Lipp, Wolfgang J. Schnedl, Heinz F. Hammer, Peter Kotanko, Georg Leb and Guenter J. Krejs

Divisions of Nuclear Medicine, Diabetology and Gastroenterology, Departments of Internal Medicine, Karl-Franzens-University, Graz; and Barmherzigen Brüder Hospital, Graz, Austria

This study investigated the prevalence of accelerated gastric emptying in 40 consecutive nonselected patients with longstanding insulin-dependent diabetes mellitus (range 11–54 yr; mean 27 yr). **Methods:** The gastric emptying of a semisolid meal labeled with ^{99m}Tc was continuously recorded with a dual-head gamma camera for 90 min in patients who were supine. **Results:** Eleven patients demonstrated delayed gastric emptying, but three male diabetics showed accelerated gastric emptying with retention values that were different from controls already after 10 min of recording (89% ± 3% versus 96% ± 4%; $p < 0.02$). During the 90-min segment, accelerated gastric emptying reduced initial gastric contents to 11% ± 8% ($p < 0.001$) as compared to 50% ± 10% in control subjects and 78% ± 6% ($p < 0.001$) in patients with delayed gastric emptyings. Accelerated gastric emptying was characterized by an almost equal initial meal distribution in proximal and distal compartments of stomach, both emptying approximately 90% of their contents within 90 min. Normal and delayed gastric emptying was characterized by a 60%–40% initial ratio of meal distribution between gastric compartments. During normal emptying, both compartments reduced contents with approximately 50%, but delayed gastric emptying was caused by only a 15% reduction of proximal contents accompanied by a 34% reduction in distal contents. **Conclusion:** Recording in the supine position to abolish gravitational influences demonstrated accelerated gastric emptying of a firm semisolid meal with a prevalence of 8%. However, delayed gastric emptying was shown as the predominant gastric manifestation of longstanding insulin-dependent diabetes mellitus with a prevalence of 28%.

Key Words: accelerated gastric emptying; insulin-dependent diabetes mellitus; supine position; semisolid test meal

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For correspondence or reprints contact: Rainer W. Lipp, MD, Division of Nuclear Medicine, Dept. of Internal Medicine, Auenbruggerplatz 15, A-8036 Graz, Austria.