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Technetium-99m-L,L-ethylenedicysteine scintigraphy in patients with renal disorders

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Abstract. Technetium-99m-L,L-ethylenedicysteine (^{99m}Tc-L,L-EC), a new renal imaging agent, was introduced as an alternative to ^{99m}Tc-mercaptoacetyltriglycine (MAG3). This radiopharmaceutical can be easily labelled at room temperature and has high radiochemical purity and long stability. The aim of this study was to gain clinical experience in using ^{99m}Tc-L,L-EC in normal volunteers and patients. The clearance of this radiopharmaceutical was compared with that of iodine-131 *ortho*-iodohippurate (OIH) in five healthy volunteers. In addition, conventional renogram and whole-body distribution of ^{99m}Tc-L,L-EC (40 min and 3 h post-injection) were evaluated in these subjects. Subsequently, ten patients with suspected obstructive nephropathy, four with renovascular disorders and two in acute renal failure were imaged. In five patients with impaired renal function both ^{99m}Tc-MAG3 and ^{99m}Tc-L,L-EC studies were performed. In each case the scintigraphic images and time/activity curves were evaluated and various semiquantitative parameters calculated and compared. No adverse effects were noted during and after ^{99m}Tc-L,L-EC scintigraphy. The mean clearance values for ^{99m}Tc-L,L-EC and ^{131}I-OIH in volunteers were 504 and 663 ml/min respectively. The total plasma clearance of ^{99m}Tc-L,L-EC was about 75.8% of the ^{131}I-OIH value. In volunteers the parenchymal transit time index, whole kidney transit time index and mean parenchymal transit time for ^{99m}Tc-L,L-EC were 63 s, 124 s and 175 s respectively. The mean time to peak activity was 235 s and the time from peak to 50% of peak activity was 402 s. In all patients the results of scintigraphy were concordant with clinical findings and subsequently influenced patient management. Furthermore, ^{99m}Tc-L,L-EC scintigraphy provided high-quality images similar to those obtained with ^{99m}Tc-MAG3, even at low glomerular filtration rates (18 ml/min). It is concluded that ^{99m}Tc-L,L-EC has excellent imaging characteristics similar to ^{99m}Tc-MAG3 and excretion properties similar to OIH. This radiopharmaceutical can be used routinely to evaluate patients with renal disorders.

Key words: Technetium-99m-L,L-ethylene dicysteine – Technetium-99m-mercaptoacetyltriglycine – Renal disorders

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Introduction

Technetium-99m labelled renal radiopharmaceuticals continue to be evaluated as substitutes for radioiodinated *ortho*-iodohippurate (OIH, Hippuran). Many ^{99m}Tc-labelled renal agents have been assessed and proposed as substitutes for iodine-131 labelled OIH during the last decade. The main limitations of using ^{131}I-OIH for renal scintigraphy are poor image quality and high radiation dose, especially in patients with obstructive nephropathies and impaired renal function [1]. ^{123}I-OIH is a nearly ideal renal radiopharmaceutical in terms of biological and radiation characteristics, but suffers from limited availability and high cost. ^{99m}Tc-mercaptoacetyltriglycine (MAG3) was shown to be a suitable replacement for ^{123}I-OIH for imaging, but not for accurate estimation of renal plasma flow [2–4]. Recently, a new tracer agent, ^{99m}Tc-L,L-ethylenedicysteine (^{99m}Tc-L,L-EC), has been proposed for renal imaging [5]. ^{99m}Tc-L,L-EC is a diacid derivative of the brain perfusion agent ^{99m}Tc-ethyl cysteinate dimer and contains an oxotechnetium-glycine sequence which structurally resembles the carbonylglycine side chain of Hippuran [5]. Initial results in volunteers have shown that the plasma clearance of ^{99m}Tc-L,L-EC was higher than that of MAG3 by a factor of 1.25 [6].

The purpose of this study was to evaluate the use of ^{99m}Tc-L,L-EC in healthy volunteers and patients with renal disorders.

Materials and methods

The study was approved by the Hospitals Clinical Trials Committee and Administration of Radioactive Substances Advisory Committee.

Five normal volunteers and 16 patients (aged 30–50 years) were included in this study. Patients under 14 and pregnant women were excluded.

Radiopharmaceutical preparation. ^{99m}Tc-L,L-EC was prepared by reconstitution of a labelling kit. The kit contained two vials (vials A and B). Vial A contained 0.5 mg of L,L-EC, 10 mg of $Na_2HPO_4 \cdot 2H_2O$, 45 mg of $Na_3PO_4 \cdot 12H_2O$ and 0.1 mg of $SnCl_2 \cdot 2H_2O$ in lyophilised form. Vial B contained a 0.545 *M* solution of $NaH_2PO_4 \cdot 2H_2O$ in water for injections. Labelling was carried out under aseptic conditions. 1000 MBq of sodium pertechnetate in a volume not exceeding 5 ml was added to the vial which contained L,L-EC. After 15–30 s 0.25 ml of buffer from vial B was added. The mixture was left standing at room temperature for 10–12 min. The pH of the prepared radiopharmaceutical was between 7.5 and 8.5. Similarly, in all the preparations free pertechnetate and colloidal ^{99m}Tc were both less than 2% as determined by thin-layer chromatography [5].

^{131}I-Hippuran was obtained from commercial sources (Amersham Interational plc).

Administered doses. In normal volunteers, 80–100 MBq of ^{99m}Tc-L,L-EC along with 2 MBq of ^{131}I-Hippuran was given intravenously. In patients, 80–100 MBq of ^{99m}Tc-L,L-EC alone was given. In five patients 80 MBq of ^{99m}Tc-MAG3 was also given after a 1-day interval to acquire renal studies for comparison.

Procedure. The individual was placed in the supine position with a gamma camera (GE X/CT) beneath the patient, making sure that both kidneys and heart were in the field of view. A 19-gauge intravenous cannula was placed in an antecubital vein, connected to a three-way stop-cock and properly secured with tape after checking that the cannula was in the vein. ^{99m}Tc-L,L-EC was injected as a bolus, mediated by 10 ml of saline flush.

Renogram acquisition and analysis. After the bolus injection of the radiopharmaceutical, dynamic images were acquired on a computer; initially the frame rate was one per second for 40 s (subsequently these were reframed for 10 s) and then 146 frames were acquired at a rate of 10 s each. A 128×128 word pixel matrix was used for acquisition.

If it was clinically adjudged that there was retention of radiotracer in the pelvicalyceal system, frusemide was administered intravenously approximately 15 min into study, in a dose of 0.5 mg kg^{-1} body weight.

The scintigraphic images and computer-generated time-activity curves were analysed and the following parameters were calculated: split renal function (percentage of total uptake in the left and right kidneys), time to peak, time from peak to 50% of peak activity and percentage residual activity in each kidney at the end of the study. In addition, by utilising the first 15 min of

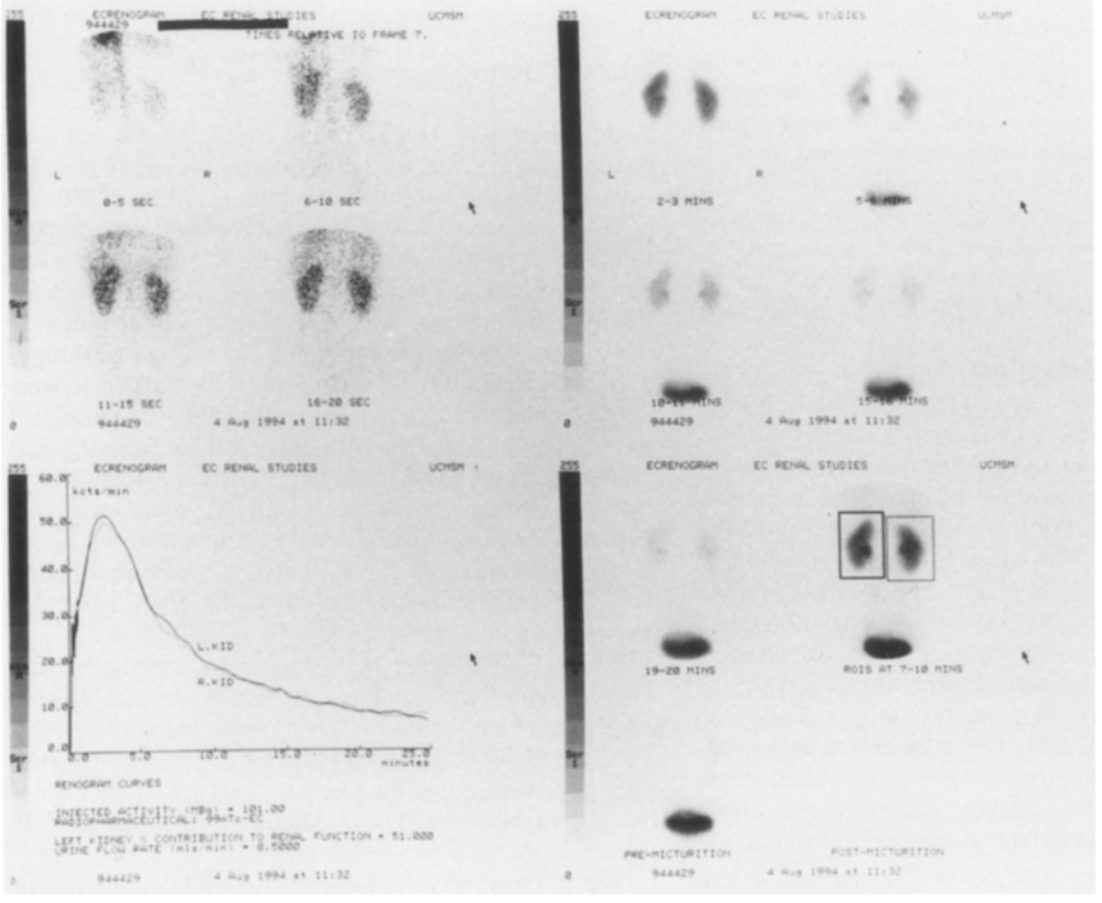


Fig. 1. ^{99m}Tc-L,L-EC renal study in a normal volunteer. Images show angiographic phase, uptake and excretory phase and time-activity curves for both kidneys

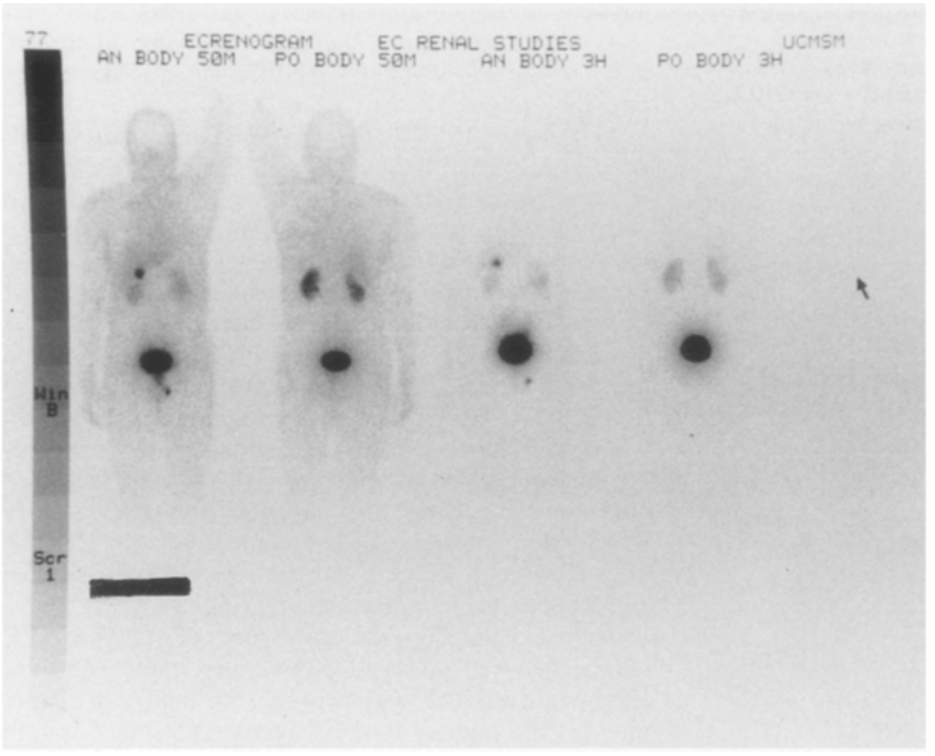


Fig. 2. ^{99m}Tc-L,L-EC study in a normal volunteer. Anterior and posterior whole-body images at 40–50 min and 3 h post-injection showing gall-bladder and faint liver activity which decreases with time

Table 1. Differential function and transit time indices in patients with suspected obstruction

No.	Kidney	% Function	PTTI (s)	WKTTI (s)	MPTT (s)	Time to peak (s)	Time from P to 1/2P (s)	Residual % at 25 min
1	Left	72	105	275	205	370	640	26
	Right	28	127	668	247	1110	–	91
2	Left	47	179	322	259	250	1050	30
	Right	53	88	153	168	190	609	20
3	Left	67	161	275	241	370	800	20
	Right	33	328	442	428	870	460	42
4	Left	44	91	126	251	270	750	24
	Right	56	111	209	191	270	970	28
5	Left	79	79	89	159	170	550	26
	Right	21	128	126	248	230	730	38
6	Left	42	92	141	192	290	870	18
	Right	58	54	80	214	210	730	19
7	Left	63	29	39	289	170	490	13
	Right	37	511	610	610	670	680	44
8	Left	32	481	677	661	1370	–	97
	Right	68	308	536	388	1050	–	87
9	Left	49	23	78	263	190	400	30
	Right	51	56	88	136	170	310	14
10	Left	49	133	208	213	230	600	21
	Right	51	32	56	232	190	480	19

P, Peak activity; 1/2P, 50% of peak activity; PTTI, parenchymal transit time index (normal range<156 s); WKTTI, whole kidney transit time index (normal range<170 s); MPTT, mean parenchymal transit time (normal range<240 s)

data before the administration of frusemide, deconvolution analysis with a matrix algorithm method was employed to calculate parenchymal transit time index (PTTI), whole-kidney transit time index (WKTTI) and mean parenchymal transit time (MPTT) [7].

Blood samples. An additional cannula was placed in the contralateral arm to obtain 5-ml blood samples at 2, 5, 7.5, 10, 15, 30, 45, 60, 90, 120 and 180 min post-injection. After the injection, the empty syringe was measured for the residual activity. At the end of the study, the sample tubes were centrifuged to separate the

plasma, and 2 ml of plasma was dispensed in tubes for counting. Standards for ^{99m}Tc-L,L-EC and ^{131}I-OIH were prepared at the time of dose preparation. Counting of the standards and plasma samples was done in a calibrated dual-channel counter (LKB, 1282 Compugamma). The counts obtained were plotted as a log-linear graph and the slow component of the bi-exponential curve was then used for calculation of clearance. In each case plasma clearance values were normalised to 1.73 m^2 body surface area. Glomerular filtration rate (GFR) was measured with chromium-51 ethylene diamine tetra-acetic acid and values were expressed in ml/min/1.73 m^2 body surface area.

Whole-body scans. To evaluate the distribution of ^{99m}Tc-L,L-EC within the body, anterior and posterior whole-body images were obtained at 40 min and 3 h post-injection, using a dual-headed gamma camera (G.E. Maxxus) fitted with low-energy general-purpose collimators, at a scan speed of 10 min per metre.

Statistical analysis. Student's *t*-test was performed to compare the semi-quantitative renogram parameters obtained with ^{99m}Tc-MAG3 and ^{99m}Tc-L,L-EC in patients with renal failure. A P value of<0.05 was taken as significant.

Results

Each ^{99m}Tc-L,L-EC study was evaluated for its safety and adverse effects. Since ^{99m}Tc-L,L-EC was being proposed as a new renal radiopharmaceutical, the vital signs in normal volunteers as well as patients were monitored before, during and after the procedure in all subjects. On conclusion of the study, individuals were asked to report anything unusual during the next 7 days. No adverse effects were noted during the study and none of the patients or normal volunteers reported any adverse effects after the study.

With ^{99m}Tc-L,L-EC, the heart and the great vessels were clearly seen during the angiographic (first) phase of the renogram. Renal activity due to blood flow was clearly demonstrated in the first 10 s post-injection. Renal pelvic activity was seen in all normal volunteers by 5–6 min. One could clearly visualise the urinary bladder by 10–11 min post-injection. No extrarenal activity was noted during the period of study, i.e. 25 min. Maximum activity of the radiotracer was seen in the kidneys between 2 and 3 min, and then progressively decreased with time. The background activity decreased as the renogram progressed, while the bladder activity increased over this time. There was minimal to no liver activity noted during the period of renogram acquisition (Fig. 1). The 40–50 min anterior whole-body images showed gall-bladder and faint liver activity (Fig. 2).

In the volunteers the clearance of ^{99m}Tc-L,L-EC ranged between 425 and 574 ml per minute and for Hippuran clearance was between 553 and 736 ml per minute. The ratio of L,L-EC/Hippuran clearance was in the range of 0.69–0.80 (mean=0.75).

In the volunteers, the percentage relative function of the kidneys varied between 42% and 58%. The PTTI was between 39 and 97 s (mean 63 s), WKTTI ranged between 59 and 270 s (mean=124 s) and MPTT was between 125 and 206 s (mean=175 s). Peak activity was

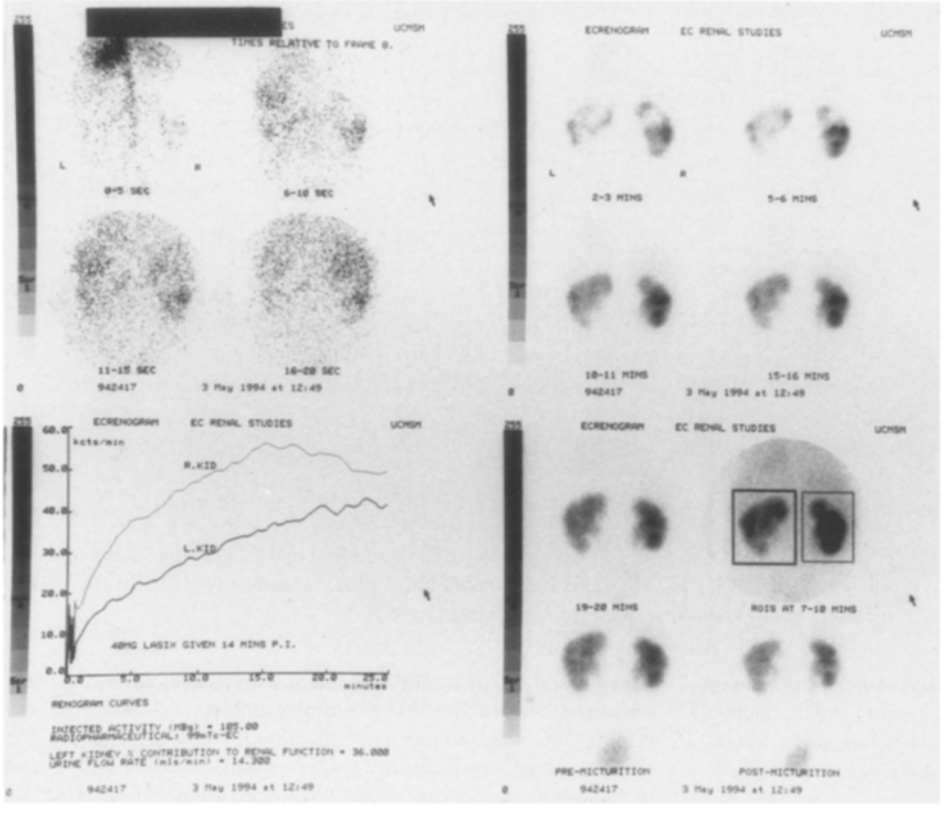


Fig. 3. ^{99m}Tc-L,L-EC renal study in a patient with bilateral obstructive nephropathy (GFR of 40 ml/min/1.73 m^2 body surface area). *Upper left and right quadrants* show renal activity at various times; *lower left and right quadrants* show time-activity curves and pre- and post-micturition images respectively

reached between 150 and 350 s (mean=235 s) and time to fall from peak activity to its half value varied between 240 s and 940 s (mean 402 s). Percentage residue of the peak activity at the end of 25 min (the time of total renogram) ranged between 15% and 42% (mean=22.3%).

Of the 16 patients, ten were referred for suspected obstructive nephropathy (three were in chronic renal failure), four were referred for evaluation of possible renovascular disease and two were in acute renal failure.

Of the ten patients with suspected obstruction, four (five kidneys) were diagnosed as having obstructive nephropathy based on the renogram and PTTI (Table 1). Of these, patients 2 and 3 underwent pyeloplasty. The renographic findings and transit times of patients 3 with obstructive nephropathy are shown in Fig. 3. Patient 8, with bilateral obstruction, had bilateral nephrostomies to relieve the obstruction.

In the four patients referred for suspected renal vascular hypertension (Table 2), a captopril study was performed. The duration of hypertension in these patients varied between 1 and 6 years. Furthermore, patients 11 and 13 were in chronic renal failure and the renogram images showed a high background which reflected the clinical status of the patients. The renogram studies showed that there was no evidence that angiotensin II-dependent renovascular dysfunction was responsible for the hypertension. In these four patients ACE inhibition therapy was initiated and their blood pressure improved significantly.

In both of the patients (15, 16) referred for evaluation of acute renal failure post-surgery, the renograms showed progressive accumulation of tracer in the kidneys with a rising time-activity curve and virtually no excretion of tracer, this pattern being typical of acute tubular necrosis (Fig. 4). In both cases time to peak, time from peak to 50% of peak activity and percentage residual activity in each kidney at the end of the study were not calculated.

Table 2. Clinical data for patients with renovascular disorders and renal failure

No.	History/complaints	GFR (ml/min)	Creatinine (μmol/l)	ER activity
11	CRF, HT, right renal bruit	20	260	High background
12	HT, renal artery stenosis?	64	154	Nil
13	CRF, HT	24	326	High background
14	HT	70	168	Nil
15	Polyarteritis nodosa/aneurysm repair	–	546	High background
16	HT/aneurysm repair	–	712	High background

CRF, Chronic renal failure; HT, hypertension; GRF, glomerular filtration rate (in ml/min/1.73 m^2); ER, extrarenal activity

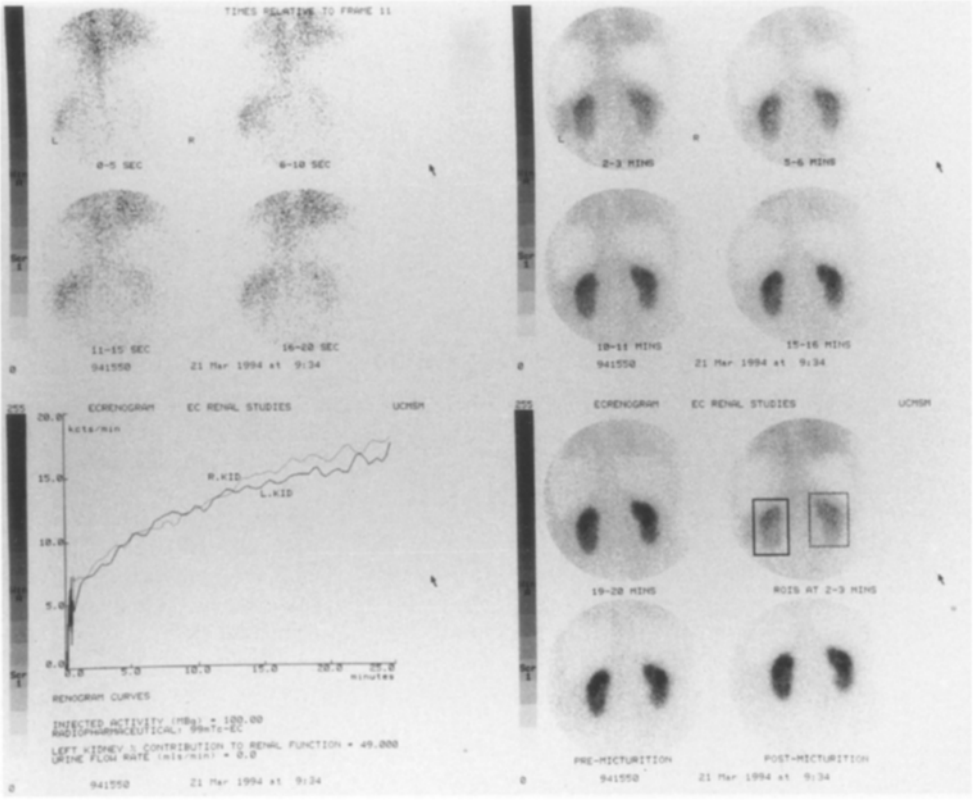
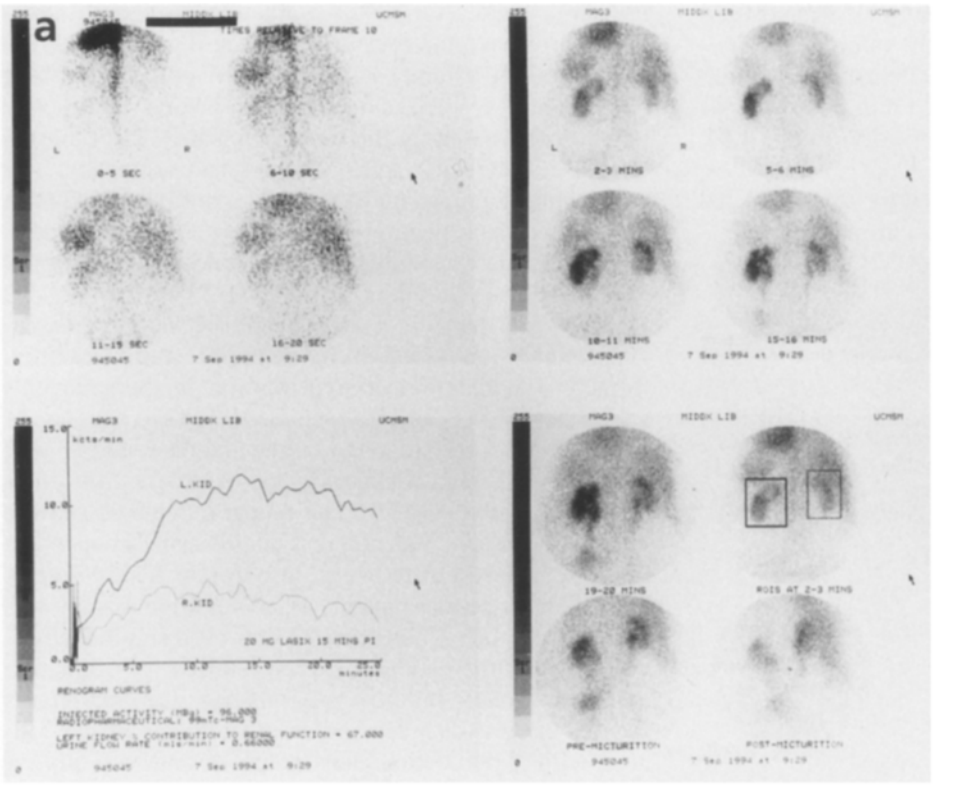


Fig. 4. ^{99m}Tc-L,L-EC renal study of a patient in renal failure due to acute tubular necrosis. The patient also had large bilateral pleural effusions, which on the images appear as photon-deficient areas in the lower part of chest



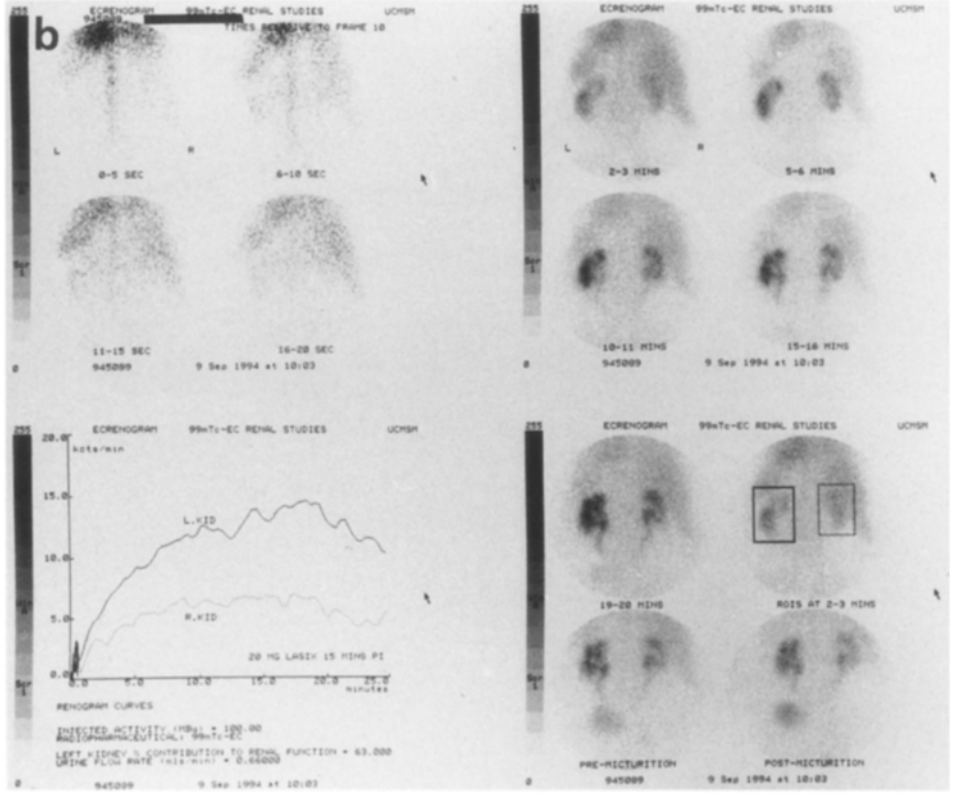


Fig. 5. A ^{99m}Tc-MAG3 and ^{99m}Tc-L,L-EC renal study in a patient with suspected obstructive nephropathy and chronic renal failure (GRF=18 ml/min/1.73 m^2 body surface area). Faint liver activity is noted on both studies

In five patients (3, 4, 8, 11 and 13) a ^{99m}Tc-MAG3 study was also performed for comparison with ^{99m}Tc-L,L-EC. These patients were in chronic renal failure. There was no significant difference in image quality, time-activity curves (Fig. 5) and other semiquantitative indices [PTTI, WKTTI, MPTT, time to peak, time from peak to 50%, and percentage residual activity ($P>0.05$)] between the two studies in these patients.

Discussion

This study shows that ^{99m}Tc-L,L-EC is a suitable tracer for routine renal scintigraphy, as it yields high-quality images comparable to those provided by ^{99m}Tc-MAG3.

^{99m}Tc-L,L-EC is a new ^{99m}Tc complex, based on a diamine dithiol ligand backbone. We found that ^{99m}Tc-L,L-EC was easy to prepare. It was available in a kit formulation, did not need a boiling step and was stable at room temperature throughout the day. Verbruggen and coworkers [5] have shown that only a single stereo isomer is formed upon complexation and side products are negligible. Furthermore, the renal excretion of ^{99m}Tc-L,L-EC in mice, baboons and human volunteers was fairly good [5, 6]. We observed that ^{99m}Tc-L,L-EC gives a typical three-phase renogram with major extraction by the kidneys. The renal images showed a high kidney to background ratio, rapid disappearance from the vascular system, limited uptake in the extra-renal organs and low residual activity in kidneys after 30 min. The faint activity observed in liver and gall-bladder at 40–50 min was not surprising. This probably represents normal biodistribution of this tracer. However, this uptake did not interfere with the images during the renogram phase even in patients with severely impaired renal function.

In this study the clearance of ^{99m}Tc-L,L-EC was measured using the slow component of the double compartment model. This was to obtain a range of values which could be compared with those obtained from patients with impaired renal function. The clearance value of ^{99m}Tc-L,L-EC was found to be 75.8% of that of OIH, which is similar to the clearance values reported by other investigators [6, 8]. It has also been reported that the clearance values of ^{99m}Tc-L,L-EC are generally higher than those of ^{99m}Tc-MAG3 by a factor of 1.25 [6]. Furthermore, the plasma protein binding is low for ^{99m}Tc-L,L-EC and high for ^{99m}Tc-MAG3, whereas Hippuran has an intermediate value. The urinary excretion is comparable for all agents. It is assumed that the higher volume of distribution together with the large fraction filtered by the glomeruli contributes mainly to the higher plasma clearance of ^{99m}Tc-L,L-EC [5]. Additional information like the renal extraction efficiency may be helpful to further clarify the kinetics of this new renal tubular agent.

The results of the renographic studies with ^{99m}Tc-L,L-EC were found to be concordant with clinical findings and subsequent management was influenced by scintigraphy. We have also shown that in chronic renal failure there was no significant difference in image quality or transit time indices between ^{99m}Tc-MAG3 and ^{99m}Tc-L,L-EC studies. Thus it is quite clear that in chronic renal failure even with low GFRs, ^{99m}Tc-L,L-EC provides high-quality images, similar to those obtained with ^{99m}Tc-MAG3.

To our knowledge, until now nobody has used ^{99m}Tc-L,L-EC to evaluate patients with suspected renovascular hypertension. We used this new radiopharmaceutical in four such patients and found that this tracer gave interpretable renographic images even when the renal function was severely impaired and that the data were in concordance with the clinical condition of the patient. Based upon the report of renal scintigraphy none of the patients underwent further invasive investigations. It is difficult to say that none of these patients had renal artery stenosis (RAS). However, these patients were started on ACE inhibitors and their hypertension was controlled on ACE inhibitors without any deterioration in renal function. Thus, it can be assumed that none of these patients had functionally significant RAS.

Renal scintigraphy plays an important role in evaluating acute causes of renal failure. A common indication in this context is acute tubular necrosis. Tubular agents are excellent tools to evaluate these patients and to follow the effect of treatment or advancing disease. In this study the two patients referred for scintigraphy were in renal failure secondary to abdominal aortic aneurysm surgery. In both cases ^{99m}Tc-L,L-EC scintigraphy showed relative preservation of flow and progressive cortical accumulation of tracer in kidneys; this implied that acute tubular necrosis was the cause of renal insufficiency and it was proven so on biopsy. Subsequently, both patients recovered from acute tubular necrosis on conservative management.

No side-effects were experienced by any of the subjects who participated in this study. This observation is in confirmation of other studies, which have not reported any direct side-effects due to administration of ^{99m}Tc-L,L-EC [5, 8, 9].

In this study no attempt was made at dosimetry. In the literature, no definite dosimetry has to date been documented for this radiopharmaceutical. For this study we presumed that the dosimetry would be similar to that of ^{99m}Tc-MAG3 (EDE=1 mSv), and as the clearance of ^{99m}Tc-L,L-EC is faster than that of ^{99m}Tc-MAG3, ^{99m}Tc-L,L-EC should provide a lower radiation dose than ^{99m}Tc-MAG3, presuming the ^{99m}Tc dose to be equal.

In conclusion, studies in volunteers and patients have indicated that ^{99m}Tc-L,L-EC is a reliable renal radiopharmaceutical that provides high-quality images and a low radiation dose to patients. It is felt that widespread use of this radiopharmaceutical will ultimately depend upon its cost.

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