Technetium-99m-N,N-Ethylenedicysteine—A Comparative Study of Renal Scintigraphy with Technetium-99m-MAG3 and Iodine-131-OIH in Patients with Obstructive Renal Disease

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Technetium-99m-labeled N,N-ethylenedicysteine (^{99m}Tc-EC) is a new renal imaging agent introduced as an alternative for ^{99m}Tc-labeled mercaptoacetyltriglycine (^{99m}Tc-MAG3), with similar renal excretion characteristics. To evaluate the diagnostic characteristics of this agent, a gamma camera study was performed. **Methods:** Sixteen patients with obstructive renal disease and six normal controls were injected with 90 to 110 MBq of ^{99m}Tc-EC and 7.4 MBq ^{131}I-labeled orthoiodohippurate (OIH). Serial images were obtained during 20 min for ^{99m}Tc-EC and 30 min for OIH. The study was repeated using 90 to 110 MBq ^{99m}Tc-MAG3 during the same week. **Results:** Renograms, functional ratios and urinary excretion patterns of all three agents were similar. The mean time to peak activity values for OIH, ^{99m}Tc-EC and ^{99m}Tc-MAG3 were 4.25 ± 0.37 min, 4.39 ± 0.32 min and 4.00 ± 0.24 min, respectively. The time from peak to 50% activity values for OIH, ^{99m}Tc-EC and ^{99m}Tc-MAG3 were 5.48 ± 0.80 min, 6.93 ± 0.69 min and 7.33 ± 0.85 min, respectively. **Conclusion:** It is concluded that ^{99m}Tc-EC has excellent imaging characteristics and similar excretion properties to OIH. The advantages of ^{99m}Tc-EC over ^{99m}Tc-MAG3 are lower hepatobiliary uptake and simplicity of preparation.

Key Words: ethylenedicysteine; MAG3; OIH; renogram

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Radioiodinated orthoiodohippurate (OIH) is considered the principal agent for functional renal studies. Because of its high extraction efficiency, it is useful in evaluating patients with impaired renal tubular function (*1*). The major disadvantage of OIH labeled with ^{131}I is the high radiation absorbed dose, especially in patients with urinary obstruction, and poor scintigraphic imaging quality because of the high energy of the gamma rays (364 keV) (*2*). Iodine-123-labeled OIH has better physical characteristics, but the logistical problems and cost of this short-lived, cyclotron-produced radionuclide are the major reasons for its limited use in routine clinical practice (*2,3*).

The radiopharmaceutical ^{99m}Tc-mercaptoacetyltriglycine (^{99m}Tc-MAG3) has been introduced as a substitute for OIH with similar pharmacokinetics and human renogram patterns (*4–8*). On the other hand, there are significant differences between the biologic behavior of ^{99m}Tc-MAG3 and OIH. The plasma protein binding of ^{99m}Tc-MAG3 is relatively high. Its plasma clearance in humans is not higher than about 65% of the OIH clearance, and the accurate renal plasma flow estimation with ^{99m}Tc-MAG3 is relatively difficult (*8–13*).

Recently, a new ^{99m}Tc-labeled agent, ^{99m}Tc-ethylenedicysteine (EC) was developed as a substitute for OIH by Verbruggen et al. (*14–16*). Excreted from the kidney by active transport, it is easily labeled with ^{99m}Tc at room temperature (*16,17*). In humans, ^{99m}Tc-EC has similar extraction, excretion and renogram patterns as does ^{99m}Tc-MAG3. The radiopharmaceutical ^{99m}Tc-EC has higher plasma clearance and lower hepatobiliary localization than ^{99m}Tc-MAG3, and its plasma binding properties are less than those of OIH (*14–17*).

The purpose of this study was to evaluate ^{99m}Tc-EC in obstructive renal disease with various degrees of renal impairment and to compare this agent with ^{99m}Tc-MAG3 and OIH.

MATERIALS AND METHODS

Patients

Sixteen patients with obstructive renal disease who had proven or suspected hydroureteronephrosis (10 women and 6 men), mean age 34.2 yr (range 19–47 yr), were selected as the study group from the patients who were referred to this department for renal investigations. All of them had undergone urographic examinations prior to the study, which demonstrated hydroureteronephrosis and/or urolithiasis. Serum creatinine levels were in the normal range in all patients (0.4–1.4 mg/dl). In addition, six normal volunteers (two women and four men), mean age 27.4 yr (range 17–41 yr) were studied as a control group. The study protocol was approved by the Medical Faculty Ethical Committee.

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TABLE 1
Time to Peak Activity, Time from Peak to 50% Activity and Relative Renal Functional Parameters of Patients

Patient no.		t_{max} (min)			$t_{1/2}$ (min)			RF (%)		
		OIH	EC	MAG3	OIH	EC	MAG3	OIH	EC	MAG3
1	R	8	5.5	5.6	12.7	12	9	43	45	51
	L	4	4.5	4.3	5.7	7	11	57	55	49
2	R	3	3.5	6.66	9.9	10	12	90	92	94
	L	5	5.16	3.66	10.8	13	12	10	8	6
3	R	4.9	5.16	4	7.3	7	7	52	51	46
	L	5	3.83	3.3	5.9	6	6	48	49	54
4	R	—	—	—	—	—	—	2	0	0
	L	5	4.83	7	6.4	7	5	98	100	100
5	R	*	5.83	5.66	*	19	24	*	17	22
	L	*	18.5	20	*	—	—	*	83	78
6	R	18	18.1	18	—	—	—	34	36	34
	L	4	4.5	6	5.2	11	8	66	64	66
7	R	4.3	4.5	6.33	—	—	—	50	50	51
	L	5	3.83	4.33	10	10	13	50	50	49
8	R	—	—	—	—	—	—	0	0	0
	L	5	4.5	6.33	10.8	13	20	100	100	100
9	R	4	4.33	6.33	4.2	7	9	42	59	54
	L	4	5.2	7.6	—	—	—	58	41	46
10	R	18	17.6	18.3	—	—	—	87	86	85
	L	16	25	16.6	—	—	—	13	14	15
11	R	4	8.33	4.33	4.6	12	13	71	61	80
	L	19	19.3	21	—	—	—	29	39	20
12	R	3	5	3.66	3.7	4	4.3	100	98	97
	L	1	0.6	0.5	—	—	—	0	2	3
13	R	5	5	6.66	5.9	6	7	39	42	44
	L	18	17.6	20	—	—	—	61	58	56
14	R	6	5.33	4.33	9.9	10	11	47	54	51
	L	18	12.3	10.3	—	—	—	53	46	49
15	R	6	4.66	7	5.9	6.4	8	56	54	58
	L	6	4.33	5.66	9.5	8.6	10.6	44	46	42
16	R	4	6.33	4.33	8	7	6	41	41	43
	L	7	7.6	8	—	—	—	59	59	57
Mean ± s.e.m.		7.51 ± 1.07	8.3 ± 1.12	8.19 ± 1.06	7.58 ± 0.63	9.26 ± 0.81	10.31 ± 1.13			

*OIH study was not performed.

t_{max} = time to peak activity; $t_{1/2}$ = time from peak to 50% activity; RF = relative renal function; OIH = orthoiodohippurate; EC = N,N-ethylenedicysteine; MAG3 = mercaptoacetyltriglycine.

Radiopharmaceuticals

Technetium-99m-MAG3 was prepared according to the manufacturer's (Mallinckrodt Diagnostica, Petten, Holland) instructions and heated for 10 min in boiling water after adding 900 to 1000 MBq of ^{99m}Tc. It was cooled down to room temperature. Technetium-99m-EC was properly prepared according to the manufacturer's instructions (Izınta, Hungary). Labeling quality control was performed by thin-layer chromatography, and labeling efficiency was found to be greater than 94% for both agents. Iodine-131-OIH was obtained commercially (CIS Bioindustry, France).

Gamma Camera Studies

All individuals were hydrated with 10 ml of water per kilogram of body weight prior to the studies. While the patient was in the supine position, 90 to 120 MBq of ^{99m}Tc-EC was injected through a three-way connector into an intravenous catheter, which was followed by saline flush. The same procedure was performed with 7.4 MBq of ^{131}I-OIH after the termination of the ^{99m}Tc-EC study. During the same week, the study was repeated with 90 to 120 MBq of ^{99m}Tc-MAG3 using the same protocol. One patient had a nearly total bilateral obstruction, and ^{131}I-OIH could not be administered because of ethical considerations. Imaging was performed using a large field of view Siemens (Erlangen, Germany) Basicam gamma camera with a low-energy all-purpose collimator for ^{99m}Tc studies and a medium-energy collimator for ^{131}I studies. In the posterior projection, 60 images of 1 sec/frame, 12 of 5 sec/frame and 20 of 20 sec/frame were obtained for 20 min for ^{99m}Tc-EC and ^{99m}Tc-MAG3 and 30 images of 60 sec/frame were obtained for 30 min for the OIH study using a Siemens Microdelta computer. The regions of interest were placed over the whole kidney on the first 3-min composite image. The renograms and renal functional parameters were generated using the Microdelta Computer program, with attenuation correction. Renal depth was estimated from the body weight and height of the individuals and taking the radionuclide decay and background activity into account. The function curves were scaled in cpm/MBq. Dividing the renogram curve count data by the injected dose gave a better reference for comparing different studies. Time-activity curves of the liver were also generated

TABLE 2
Time to Peak Activity, Time from Peak to 50% Activity and Relative Renal Functional Parameters of Normal Controls

Controls		t_{max} (min) OIH	t_{max} (min) EC	t_{max} (min) MAG3	$t_{1/2}$ (min) OIH	$t_{1/2}$ (min) EC	$t_{1/2}$ (min) MAG3	RF (%) OIH	RF (%) EC	RF (%) MAG3
1	R	3	3.66	4	3.3	5	8	52	50	56
	L	3	3.66	3.66	3	7	7	48	50	44
2	R	5	3.33	3	6.6	6	7	39	37	38
	L	3	3	3.33	8.4	7	6	61	63	62
3	R	4	5	4.66	6.5	8.1	15	43	44	44
	L	5	5.33	4.66	5.2	9	10	57	56	56
4	R	3	4	3.33	12	8	7	41	40	42
	L	4	4.33	3.33	3.9	6	4	59	60	58
5	R	7	5.33	6	6.9	2	8	48	48	50
	L	6	7	4	4.5	12	7	52	52	50
6	R	4	4	4	2.6	7	5	53	57	56
	L	4	4	4	2.9	6	4	47	43	44
Mean ± s.e.m.		4.25 ± 0.37	4.39 ± 0.32	4.00 ± 0.24	5.48 ± 0.80	6.93 ± 0.69	7.33 ± 0.85			

t_{max} = time to peak activity; $t_{1/2}$ = time from peak to 50% activity; RF = relative renal function; OIH = orthoiodohippurate; EC = N,N-ethylenedicysteine; MAG3 = mercaptoacetyltriglycine.

with background correction. The results of the three different agents were compared in each case individually. For each studied parameter, the mean ± s.e.m. values were also calculated.

Statistical analysis was performed using Student's paired t-test or conventional regression analysis. Any p value <0.05 was accepted as significant.

RESULTS

The analysis of parameters derived from the renogram curves showed a good correlation for all three agents. Tables 1 and 2 show the time to peak activity (t_{max}), time from peak to 50% activity ($t_{1/2}$) and relative renal function values, which were similar for all three agents. For ^{99m}Tc-EC and OIH, the correlation coefficient (r) values of $t_{1/2}$, t_{max} and renal function values were 0.82, 0.93 and 0.97, respectively. For ^{99m}Tc-MAG3 and OIH, the correlation coefficients of the same parameters were 0.80, 0.93 and 0.98, respectively (Fig. 1). The t_{max}, $t_{1/2}$ and renal function values of ^{99m}Tc-EC and ^{99m}Tc-MAG3 gave a better correlation with a coefficient of 0.95, 0.94 and 0.97, respectively (Fig. 2). No significant difference was observed between renal functional parameters obtained with the three agents, even in patients with renal impairment.

In normal controls, the mean t_{max} values for OIH, ^{99m}Tc-EC and ^{99m}Tc-MAG3 were 4.25 ± 0.37, 4.39 ± 0.32 and 4.00 ± 0.24 min, respectively. The $t_{1/2}$ values for OIH, ^{99m}Tc-EC and ^{99m}Tc-MAG3 were not significantly different (5.48 ± 0.80, 6.93 ± 0.69 and 7.33 ± 0.85 min, respectively) ($p > 0.1$).

The images obtained with ^{99m}Tc-EC and ^{99m}Tc-MAG3 were also similar, and the delineation of the kidneys was better than in the cases of OIH images. Lower background and hepatic activity were observed in the images of ^{99m}Tc-EC than in the ^{99m}Tc-MAG3 images (Fig. 3). The renogram patterns for the three agents in normal subjects (Fig. 4) and in patients with obstruction (Fig. 5) were almost identical within each group.

In cinematic display, urinary peristalsis was visualized on the ^{99m}Tc-EC and ^{99m}Tc-MAG3 studies and the tracer elimination from kidney to bladder was visible (Fig. 3).

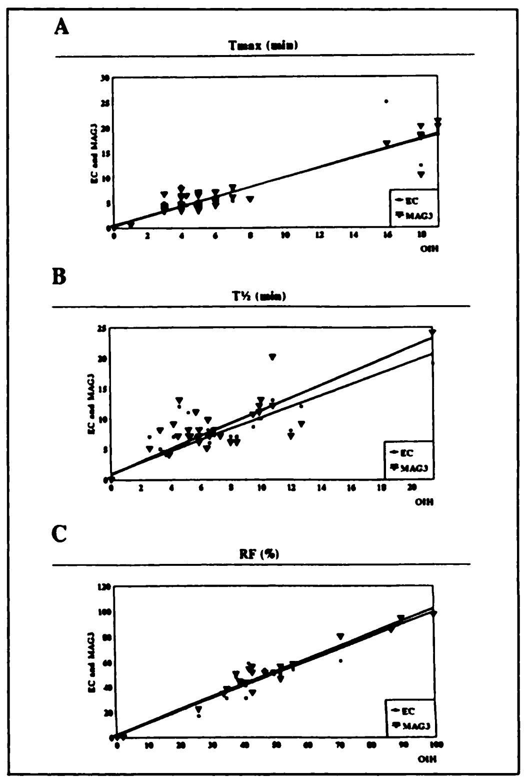

FIGURE 1. Correlation of t_{max} (A), $t_{1/2}$ (B) and right kidney relative function (RF) (C) between OIH (abscissa), ^{99m}Tc-MAG3 and ^{99m}Tc-EC (ordinate).

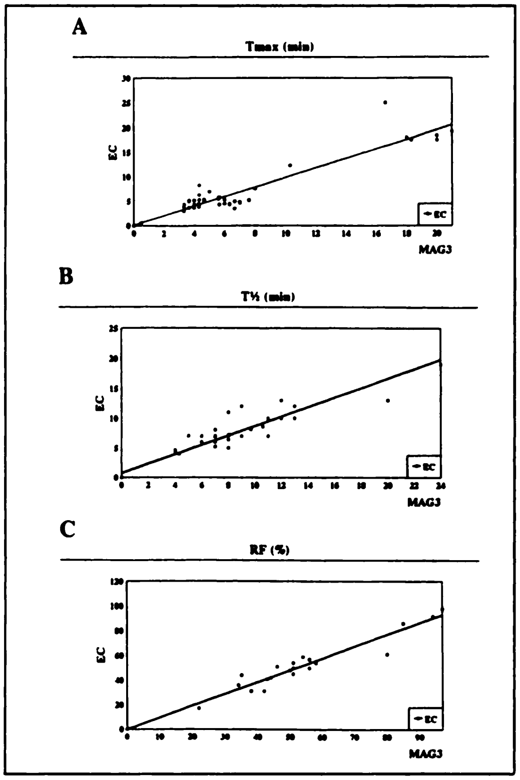

FIGURE 2. Correlation of t_{max} (A), $t_{1/2}$ (B) and right kidney RF (C) between ^{99m}Tc-MAG3 (abscissa) and ^{99m}Tc-EC (ordinate).

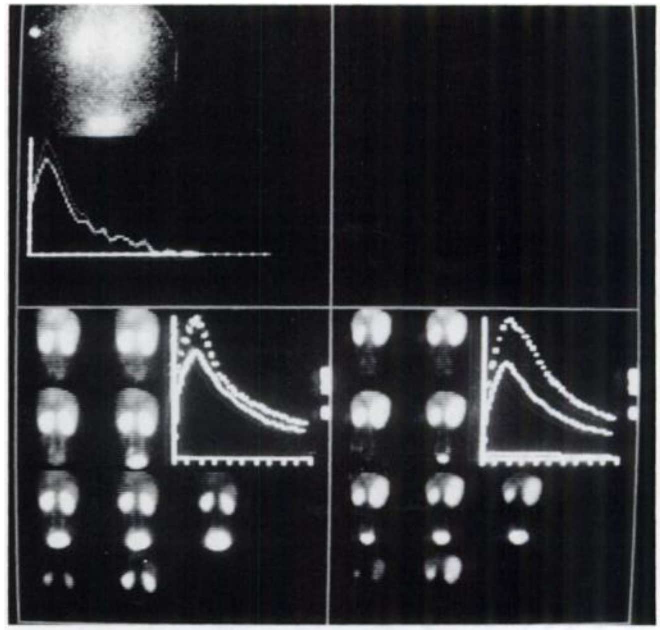

FIGURE 4. Time-activity curves of OIH (upper left corner), ^{99m}Tc-EC (lower left) and ^{99m}Tc-MAG3 in a normal control.

DISCUSSION

Various ^{99m}Tc-labeled renal agents have been proposed as substitutes for OIH during the last decade because of the poor imaging quality and high radiation dose of ^{131}I, especially in patients with obstructive uropathies (*2–5*). Presently, OIH has been largely replaced by ^{99m}Tc-MAG3 because of the excellent scintigraphic imaging quality of ^{99m}Tc (*4*). In the present study, the use of a new agent, ^{99m}Tc-EC, was investigated in renal obstructive disease in comparison with ^{99m}Tc-MAG3 and OIH.

Although a number of studies have shown strong correlations between ^{99m}Tc-MAG3 and OIH clearance, there are significant differences in their biologic behavior. The plasma protein binding of ^{99m}Tc-MAG3 is relatively high, and its plasma clearance in humans is about 65% of OIH clearance (*6–11,18–20*). Furthermore, it must not be assumed that the two agents behave similarly in every clinical situation. Taylor et al. (*8*) and Schaap et al. (*13*) reported on cases in which ^{99m}Tc-MAG3 clearance did not show proportionality to OIH clearance. These studies suggested that ^{99m}Tc-MAG3 clearance may be unreliable and ^{99m}Tc-MAG3 may not be the ideal replacement for OIH.

Gamma camera studies revealed that ^{99m}Tc-MAG3, giving high target-to-background ratios with relatively higher

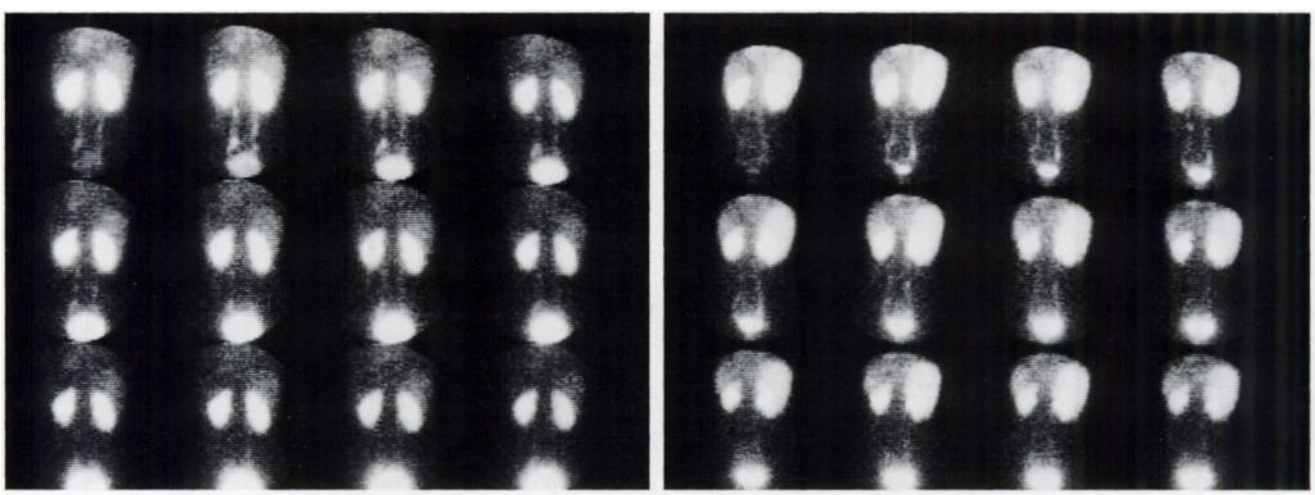

FIGURE 3. Corresponding images of ^{99m}Tc-EC (left) and ^{99m}Tc-MAG3 (right) in a patient. The delineation of the kidneys is better in the images of ^{99m}Tc-EC than those of ^{99m}Tc-MAG3 because of lower background and hepatic activity.

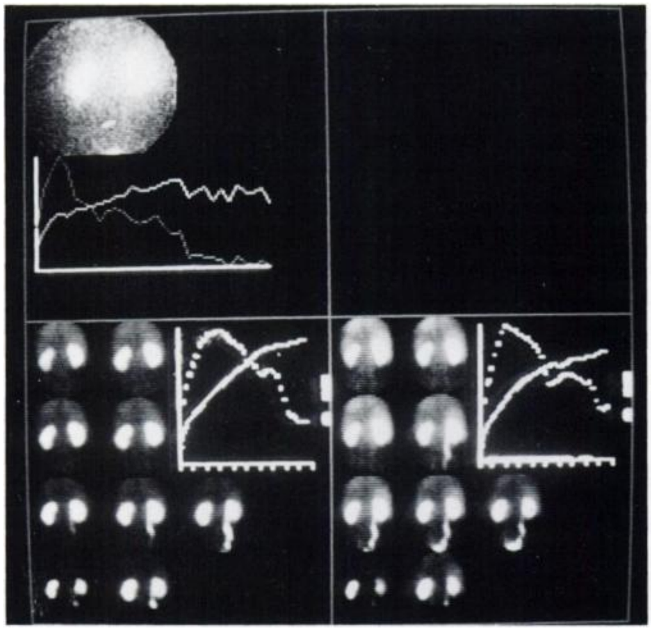

FIGURE 5. Time-activity curves of OIH (upper left corner), ^{99m}Tc-EC (lower left) and ^{99m}Tc-MAG3 in a patient with right mega-ureter (dotted lines) and left ureteropelvic obstruction (continued lines).

doses, enables better delineation of the kidneys and visualization of the ureters and their peristalsis (*8–12*). In an analysis of renogram curves, Jafri et al. (*9*), comparing ^{99m}Tc-MAG3 with OIH, found a good correlation with coefficients (r = 0.81 for parenchymal transit time index and r = 0.92 for whole-kidney transit time). In comparing the peak times of the time-activity curves, they found a correlation coefficient of r = 0.95. Russell et al. (*12*) found similar renogram patterns for ^{99m}Tc-MAG3 and OIH with a correlation coefficient of r = 0.94 for peak times. In the same study, the washout phase of the renogram was shallower for ^{99m}Tc-MAG3 than for OIH in normal kidneys. In the current findings, the correlation coefficients of ^{99m}Tc-MAG3 and OIH for $t_{1/2}$, t_{max} and renal function were in accordance with these reports (r = 0.80, 0.93 and 0.98, respectively).

In animal biodistribution studies, Verbruggen et al. (*16*) showed that renal excretion characteristics of ^{99m}Tc-EC were superior to those of ^{99m}Tc-MAG3. In their study, the accumulation of ^{99m}Tc-EC in the liver and intestines at 10 min following intravenous injection was significantly lower than that of ^{99m}Tc-MAG3. At 30 min, ^{99m}Tc-EC showed a significantly higher urinary excretion, a lower renal retention and less intestinal excretion than did ^{99m}Tc-MAG3. The 1-hr plasma clearance of ^{99m}Tc-EC in a baboon was 50% higher than that of ^{99m}Tc-MAG3. They concluded that ^{99m}Tc-EC approaches OIH more closely for the accurate determination of the effective renal plasma flow. They also reported that the scintigraphic images and renograms of ^{99m}Tc-MAG3 and ^{99m}Tc-EC obtained from the animal studies had the same clinical value. Szilvasi et al. (*17*) found a plasma clearance of 462 ± 35 ml/min/1.73 m^2 for ^{99m}Tc-EC by a modified Oberhausen method in humans. The mean plasma binding value was 28.3% ± 2.5%. In the same study, scintigraphic images demonstrated much lower hepatobiliary localization of ^{99m}Tc-EC than ^{99m}Tc-MAG3, even in patients with impaired renal function.

The current findings with gamma camera studies are in agreement with these reports. The authors performed ^{99m}Tc-EC and ^{99m}Tc-MAG3 studies during the same week assuming that a similar state of hydration was reached for each patient using a standard hydration procedure. A t_{max} value for ^{99m}Tc-EC of 4.39 ± 1.11 min and a $t_{1/2}$ value of 6.93 ± 2.40 min were found. These values were 4.20 ± 0.30 min and 9.10 ± 1.50 min, respectively, in the study of Szilvasy et al. (*17*). In the current study, equally high-quality images were acquired with ^{99m}Tc-EC as with ^{99m}Tc-MAG3. High body background and liver activity was observed in ^{99m}Tc-MAG3 images, which could be the result of the high protein binding and blood pool activity in addition to the hepatobiliary excretion of ^{99m}Tc-MAG3. The delineation of the kidney was better in ^{99m}Tc-EC images because of its lower hepatobiliary localization. Moreover, ^{99m}Tc-EC could be prepared easily at room temperature with reproducibly high labeling efficiency. In view of the close similarity of the administered radioactivity and biologic behavior of both agents, the radiation-absorbed dose to the patient for ^{99m}Tc-EC should be expected to be as low as that for ^{99m}Tc-MAG3.

In conclusion, ^{99m}Tc-EC is a suitable replacement for OIH in routine renal imaging, and it provides equally high-quality images and low radiation doses to the patient as does ^{99m}Tc-MAG3. The advantages of ^{99m}Tc-EC over ^{99m}Tc-MAG3 are lower hepatobiliary uptake and enhanced simplicity of preparation. Clinical investigations in patients with various renal diseases are needed to reach a better understanding of the renal handling and clearance of ^{99m}Tc-EC.

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