Clinical Comparison of Technetium-99m-EC, Technetium-99m-MAG3 and Iodine-131-OIH in Renal Disorders

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Technetium-99m-ethylenedicysteine has recently been developed for renal function studies. The pharmacokinetics of ^{99m}Tc-EC were studied by constant infusion technique and compared with ^{99m}Tc-MAG3 and ^{131}I-OIH in 11 patients with various renal disorders. **Methods:** After giving a 7.4 MBq ^{131}I-OIH and 90-110 MBq ^{99m}Tc-EC or ^{99m}Tc-MAG3 bolus, a constant infusion (1MBq/ml ^{99m}Tc-agent and 0.07 MBq/m ^{131}I-OIH was started. Sixteen blood and five urine samples were obtained over three hr. **Results:** The renal clearance of ^{99m}Tc-EC was higher than that of ^{99m}Tc-MAG3. The ^{99m}Tc-EC/OIH and ^{99m}Tc-MAG3/OIH ratios were 0.75 ± 0.05 and 0.55 ± 0.10 ($p = 0.00087$), respectively. The distribution volume of ^{99m}Tc-EC was also higher than that of ^{99m}Tc-MAG3 (15722 ± 4644 and 9509 ± 2788 ml/1.73m^2, respectively; $p = 0.072$). The ^{99m}Tc-EC/OIH and ^{99m}Tc-MAG3/OIH distribution volume ratios were 1.03 ± 0.14 and 0.55 ± 0.10, respectively ($p = 0.0003$). The 60-min excretion values of ^{99m}Tc-EC and ^{99m}Tc-MAG3 were compared to that of OIH. The ^{99m}Tc-EC/OIH and ^{99m}Tc-MAG3/OIH excretion ratios were 0.96 ± 0.06 and 1.07 ± 0.10, respectively ($p = 0.162$). The protein binding of ^{99m}Tc-EC and OIH were found to be 34% ± 4 and 66% ± 5, respectively ($p < 0.0001$). The red cell binding of ^{99m}Tc-EC was negligible (3% ± 1.2) in comparison to OIH (27% ± 3; $p < 0.0001$). **Conclusion:** This limited study demonstrates the pharmacokinetic and renal clearance properties of ^{99m}Tc-EC. This agent has good potential for renal function evaluation.

Key Words: iodine-131-OIH; technetium-99m-MAG3; technetium-99m-EC; renal function; renal imaging

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Because of the undesirable physical properties of ^{131}I-OIH, several ^{99m}Tc labeled renal agents have been developed during the last decade (*1–5*). Technetium-99m-MAG3 has been found the most successful compound and studied intensively (*5–14*). These studies show ^{99m}Tc-MAG3 clearance correlates strongly with OIH clearance and with all the advantages of ^{99m}Tc labeling. Technetium-99m-MAG3 is generally accepted as the agent of choice for routine renal imaging (*14–17*). However, there are significant differences between the biological behaviors of ^{99m}Tc-MAG3 and OIH (*7–12*). The plasma protein binding of ^{99m}Tc-MAG3 is relatively high and its plasma clearance in humans is about 65% of OIH. For this reason, the accurate renal plasma flow estimation with ^{99m}Tc-MAG3 is relatively difficult. These problems have led to the search for other ^{99m}Tc labeled renal tubular function agents which would provide a direct measure of effective renal plasma flow (ERPF).

Verbruggen et al. (*18*)pioneered the development of a new ^{99m}Tc labeled radiopharmaceutical L,L-ethylene-L-dicysteine (^{99m}Tc-EC) (*18*). Technetium-99m-EC is excreted from the kidney by active transport and easily labeled with ^{99m}Tc at room temperature. Plasma clearance of ^{99m}Tc-EC is reported to be higher than ^{99m}Tc-MAG3 clearance, plasma protein binding values are less than those of OIH and hepatobiliary localization is much lower than that of ^{99m}Tc-MAG3 (*18–23*). With gamma camera studies it has been shown that ^{99m}Tc-EC has comparable extraction, excretion and renogram patterns with ^{99m}Tc-MAG3 and OIH (*20,21*).

The aim of this study is to evaluate the pharmacokinetics of ^{99m}Tc-EC in various renal disorders by constant infusion technique and to compare with the values for ^{99m}Tc-MAG3 and OIH.

MATERIALS AND METHODS

Patients

Eleven patients (3 male, 8 female) age 16–52 yr with various renal disorders were selected as the study group from among patients referred to our department for renal investigations. Three patients had chronic renal insufficiency, three patients had chronic pyelonephritis, and five patients had hypertension (Table 1). The study protocol was approved by the Medical Faculty Ethical Committee.

Radiopharmaceuticals

Technetium-99m-MAG3 was prepared according to the manufacturer's instructions. Technetium-99m was obtained from a gen-

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TABLE 1
Patient Data

Patient no.	Clinical diagnosis	Sex	Age (yr)	Creatinin clearance (ml/min)
1	Chronic glomerulonephritis	F	19	38
2	Hypertension	F	39	97
3	Chronic glomerulonephritis	F	31	15
4	Hypertension	M	52	102
5	Chronic pyelonephritis	F	28	65
6	Chronic pyelonephritis	F	33	82
7	Hypertension	F	41	111
8	Chronic glomerulonephritis	M	21	38
9	Hypertension	F	46	112
10	Chronic pyelonephritis	F	16	69
11	Hypertension	M	35	118

erator. Quality control of the labeling was performed from the vial and from the infusion solution by thin layer chromatography and the labeling efficiency was found to be over 96% which stayed constant for at least three hours (*24*). Technetium-99m-EC was also prepared according to the manufacturer's instructions using 400–500 MBq of ^{99m}Tc. Labeling efficiency was found to be over 96% by thin layer chromatography which remains stable for eight hours (*18,21*). Iodine-131-OIH was obtained commercially and the free iodine was below 2% according to the manufacturer.

Clearance Studies

Patients were hydrated by regular fluid intake commencing 30 min prior to and during the study. The ^{99m}Tc-MAG3 and OIH were studied simultaneously in the first five patients. The ^{99m}Tc-EC and OIH were studied simultaneously in the next six patients. After an intravenous priming dose of 90–110 MBq of ^{99m}Tc agent and 7.4 MBq of OIH, continuous infusion (Abbott/Shaw Life care pump, model 3, Illinois) was started at a rate of 30 ml/hr containing 1 MBq/ml of ^{99m}Tc agent and 0.07 MBq/ml of OIH for a period of 180 min. In the first, third and eighth patients loading dose and continuous infusion rate were reduced according to the creatinine clearance of these patients (*25*). The same procedure was performed within the same week for the other ^{99m}Tc agent alone. Sixteen 2-ml blood samples were withdrawn at 5, 10, 15, 20, 25, 30, 40, 50, 60, 75, 90, 105, 120, 140, 160 and 180 min from the forearm opposite the injection arm. Before drawing each blood sample, a three-way connector was washed with saline, 2 ml of blood was withdrawn and reinjected into the patient after obtaining the actual sample. The blood samples in heparinized tubes were centrifuged and 0.2 ml of plasma radioactivity was measured in a gamma counter (Cobra II, Packard). For simultaneous measurements a cross-talk correction of ^{131}I into the ^{99m}Tc channel was performed. Standards of OIH, ^{99m}Tc-EC and ^{99m}Tc-MAG3 were prepared at the time of dose preparation and the injected doses were estimated from the standard activity and weight difference of each syringe before and after injection.

By spontaneous voiding, urine was collected at 30, 60, 90, 120 and 180 min and urine radioactivity was determined by counting 0.2 ml urine samples. Post-void bladder residual urine correction was not performed.

Pharmacokinetic Analysis

Renal clearance was calculated using the following equation (*26*):

$$\text{Renal clearance} = [U] \times V_{t1 \to t2} \Big/ \int [P]\, dt_{t1 \to t2}\ (\text{ml/min}), \quad \text{Eq. 1}$$

where U represents the urinary concentration (cpm/ml), V represents the total urinary volume (ml) excreted during steady-state, $_{t1 \to t2}$ is the steady-state interval and P represents the plasma concentration (cpm/ml). Total-body clearance was also calculated from (*27*):

$$\text{Total-body clearance} = D_{\text{inf } t1 \to t2} \Big/ \int [P]\, dt_{t1 \to t2}\ (\text{ml/min}), \quad \text{Eq. 2}$$

where $D_{\text{inf } t1 \to t2}$ is the total amount of activity administrated during the steady-state (cpm) and P is the plasma concentration (cpm/ml). Distribution volume was calculated using the following equation (*28*):

$$\text{Distribution volume} = \text{Amount of activity in body/C}, \quad \text{Eq. 3}$$

where C represents the plasma concentration achieved during steady state. Amount of activity in the body is determined from the difference of the activity administered and activity excreted (*29*).

Excretion fraction was calculated by the amount of ^{99m}Tc-MAG3, ^{99m}Tc-EC and ^{131}I-OIH excreted in 0–60 min period expressed as a percentage of administered dose.

The plasma protein binding values of ^{99m}Tc-EC and ^{131}I-OIH were determined from the 20 min plasma samples by ultrafiltration (Ultrafree-PFL filter units, type UFP2 LGC 24, Milipore).

Red blood cell (RBC) binding values were calculated for ^{99m}Tc-EC and ^{131}I-OIH from the 20 min blood samples by counting the whole blood and correcting for the plasma count and hematocrit (Htc) (RBC binding = whole blood cpm/ml − (plasma cpm/ml × plasma Htc)) (*30*). Htc was determined from the mean corpuscular volume and RBC amount (Medonic, cell analyser CA610, Sweden). RBC amount was determined by a dilution and electric resistance detection technique in which plasma trapping between RBCs most likely did not effect the results (*10*).

Statistical analysis was performed using the Student's unpaired two-tailed t-test and a value of $p < 0.05$ was accepted as significant.

RESULTS

Table 1 demonstrates the patient data. Six patients were hospitalized during the 1-wk study interval. These patients were strictly controlled regarding the daily water intake and urine output, the alimentation and laboratory investigations including serum creatinine and protein levels and urine analyses. The remaining five patients (hypertensive) were controlled with serum creatinine levels and urine analyses. No alterations were documented in clinical and laboratory states of the patients during this time interval. Two patients (Patients 7 and 9) refused to participate in the second part of the experiment, the ^{99m}Tc-MAG3 evaluation.

Constant plasma levels were obtained for each patient at ~70–90 min, except for the first patient with high volume distribution (Table 2) who reached constant plasma level at 120 min.

TABLE 2
Distribution Volume (VD) of OIH, ^{99m}Tc-EC and ^{99m}Tc-MAG3 (ml/1.73 m^2)

Patient no.	OIH	^{99m}Tc-EC	^{99m}Tc-MAG3
1	40304	37396	17493
2	16741	13067	9890
3	—	15811	8737
4	—	10488	8155
5	9627	12851	6858
6	12600	13565	5921
7	17449	18564	—
8	11444	10127	—
9	11563	13316	—
10	—	16663	—
11	—	11095	—
mean	17104	15722	9509
s.e.m.	6727	4644	2788

(—) = could not be calculated because of data error or patient refusal.

TABLE 4
Sixty-Minute Excretion of OIH, ^{99m}Tc-EC and ^{99m}Tc-MAG$_3$ as Percentage of Administered Dose

Patient no.	OIH	^{99m}Tc-EC	^{99m}Tc-MAG3
1	25	23	31
2	53	60	60
3	—	9	13
4	—	73	70
5	63	58	68
6	74	65	60
7	69	68	—
8	36	32	—
9	65	64	—
10	—	69	—
11	71	68	—
mean	57	54	50
s.e.m.	15	18	19

(—) = could not be calculated because of data error or patient refusal.

Table 3 shows the renal and total-body clearance values of OIH, ^{99m}Tc-EC and ^{99m}Tc-MAG3. The renal clearance and the total-body clearance of ^{99m}Tc-EC were nearly equal ($p = 0.98$) as they were also identical for ^{99m}Tc-MAG3 and for OIH ($p = 0.92$ and $p = 0.94$, respectively). The mean (±s.e.m.) renal clearance of ^{99m}Tc-EC was lower than that of OIH ($p = 0.072$) with a value of 245 ± 86 ml/min/1.73m^2 and higher than that of ^{99m}Tc-MAG3 ($p = 0.20$). The ^{99m}Tc-MAG3 clearances could be obtained in 8 of 11 patients. The mean ^{99m}Tc-MAG3 clearance was 192 ± 77 ml/min/1.73m^2 which was significantly lower than that of OIH ($p = 0.0155$).

Distribution volume of ^{99m}Tc-EC was similar to OIH distribution volume ($p = 0.745$), giving a ratio of 1.03 ± 0.14 and it was significantly higher than that of ^{99m}Tc-MAG3 (0.55 ± 0.10; $p = 0.0003$). The mean distribution volumes for OIH, ^{99m}Tc-EC and ^{99m}Tc-MAG3 were 17104 ± 6727, 15722 ± 4644 and 9509 ± 2788 ml, respectively (Table 2).

The 60-min excretion fractions, expressed as a percentage of the injected dose for three agents were %57 ± 15, %54 ± 18 and %50 ± 19 for OIH, ^{99m}Tc-EC and ^{99m}Tc-MAG3, respectively (Table 4) ($p = 0.70$ and $p = 0.54$ for ^{99m}Tc-EC and ^{99m}Tc-MAG3, with respect to OIH excretion).

The half-life values derived from the total-body clearance values and distribution volume were found to be higher for ^{99m}Tc-EC as compared to OIH and ^{99m}Tc-MAG3 (Table 5) ($p = 0.162$) (*28*).

The protein bindings of ^{99m}Tc-EC ($n = 6$) and OIH ($n = 5$) were 34% ± 4% and 66% ± 5%, respectively, determined by ultrafiltration ($p < 0.0001$). RBC binding of

TABLE 3
Renal Clearance (R Cl.) and Total-Body Clearance (T Cl.) of OIH, ^{99m}Tc-EC and ^{99m}Tc-MAG3 (ml/min/1.73 m^2)

	R Cl.			T Cl.		
Patient no.	OIH	^{99m}Tc-EC	^{99m}Tc-MAG3	OIH	^{99m}Tc-EC	^{99m}Tc-MAG3
1	150	105	50	149	106	43
2	462	317	282	460	329	269
3	—	78	45	—	79	42
4	—	301	271	—	310	264
5	366	280	242	368	267	244
6	380	252	171	379	248	174
7	448	350	—	455	362	—
8	89	75	—	88	76	—
9	440	346	—	441	351	—
10	367	283	231	364	295	215
11	410	303	242	423	316	255
mean	346	245	192	347	249	188
s.e.m.	101	86	77	102	89	76

(—) = could not be calculated because of data error or patient refusal.

TABLE 5
Mean ± s.e.m. Protein Binding and RBC Binding Values of OIH and ^{99m}Tc-EC Obtained from 20-min Samples

	OIH	^{99m}Tc-EC	^{99m}Tc-MAG3
Protein binding (%)	66 ± 5	34 ± 4	—
RBC binding (%)	27 ± 3	3 ± 1.2	—
$T_{1/2}$ (relative to OIH)	—	1.38 ± 0.22	1.15 ± 0.18

$T_{1/2}$ values are expressed as the relative value to that of OIH.

^{99m}Tc-EC (n = 8) obtained from 20-min blood samples was negligible (%3 ± 1.2), whereas the RBC binding of OIH (n = 7) was found as %27 ± 3 ($p < 0.0001$) (Table 5).

DISCUSSION

It has been demonstrated that ^{99m}Tc-MAG3 clearance shows a strong correlation with OIH clearance. However, the proportionality constant has been controversial and reported to range from 0.47 to 0.95 depending upon the applied method and the purity of the kit used (*5–12*). Moreover, the biological properties of these two agents are not identical and they may behave differently under different clinical conditions (*7,31*). Although some authors have proposed a formula to convert ^{99m}Tc-MAG3 clearance to the OIH clearance (*10,13,32*), the estimation of ERPF with ^{99m}Tc-MAG3 may still be unreliable (*14*). Therefore, ^{99m}Tc-MAG3 is not the ideal replacement for OIH. This study investigated the pharmacokinetics of a new technetium-labeled renal agent ^{99m}Tc-EC which was introduced more recently (*18*).

In accordance with the report of Van Nerom et al., (*21*) in this study the distribution volume of ^{99m}Tc-EC was found similar to that of OIH ($p = 0.745$) and higher than that of ^{99m}Tc-MAG3 ($p = 0.072$ for absolute values, $p = 0.0003$ for values relative to OIH) (Table 3). The higher distribution volume of ^{99m}Tc-EC was accompanied by the lower protein binding of ^{99m}Tc-EC as compared to that of ^{99m}Tc-MAG3. The protein binding of ^{99m}Tc-EC (34%) was significantly lower than that of OIH (66%; $p < 0.0001$). Although the protein binding of ^{99m}Tc-MAG3 was not determined in this study, the reported human values range from 66% to 90%, which were higher than the values found for OIH (from 47% to 70%) (*5–12*). The RBC binding fraction was lower (3%) for ^{99m}Tc-EC as compared to OIH (27%; $p < 0.0001$). The observation of lower RBC binding of ^{99m}Tc-EC as compared to OIH may account for the similarity in their distribution volume despite different protein binding values.

The renal clearance and corresponding total-body clearance values of ^{99m}Tc-EC was not significantly different ($p = 0.98$) as well as ^{99m}Tc-MAG3 and OIH renal and total-body clearances (Table 3). This finding suggests that the extrarenal clearance, if any, has to be minimal for ^{99m}Tc-EC. Since post-void residual urine correction was not performed, the methodology seems to be prone to a slight error in determining renal clearance. Verbruggen et al. and Van Nerom et al. reported the presence of extrarenal clearance of ^{99m}Tc-EC in animals and in humans, respectively, to be lower than those of ^{99m}Tc-MAG3 and OIH (*18,21*).

The renal clearance of ^{99m}Tc-EC was 75% of OIH clearance ($p = 0.085$); however, it was higher than that of ^{99m}Tc-MAG3 ($p = 0.20$ for absolute values, $p = 0.0006$ for values relative to OIH). The higher renal clearance of ^{99m}Tc-EC with respect to ^{99m}Tc-MAG3 clearance can be attributed to the presence of glomerular filtration of ^{99m}Tc-EC as a consequence of lower protein binding with higher free fraction and higher distribution volume (*21*). Almost similar ratios with respect to OIH clearance values in healthy volunteers (*21*), in renal transplant patients (*22*) and in the patients with renal disorders (*23*) were also reported. This finding suggests that ^{99m}Tc-EC has similar biological behavior as of OIH under both normal and depressed renal functions. Therefore, it seems that ^{99m}Tc-EC clearance can be used as a parameter of kidney function and an estimation of effective renal plasma flow may be obtained with ^{99m}Tc-EC. However, it is indispensable to study the validity of this finding in a larger series and in patients with various degrees of renal impairment. Also, for a better understanding of the renal elimination mechanism differences existing between ^{99m}Tc-EC and ^{99m}Tc-MAG3, the affinity to the tubular transport system and extraction ratio of ^{99m}Tc-EC needs to be investigated.

The 60-min excretion fractions gave similar results for all three agents (Table 4). Verbruggen et al. found that 30-min excretion ratios from the kidneys were 0.90, 0.93 and 0.89 for OIH, ^{99m}Tc-EC and ^{99m}Tc-MAG3 respectively (*18*). Van Nerom et al. reported the 60-min excretion ratios of ^{99m}Tc-EC and ^{99m}Tc-MAG3 as 79.8% and 83.1%, respectively (*21*). The gamma camera studies reported previously were in accordance with these results and showed that the renogram curves and the renal functional parameters obtained from the time-activity curves were also similar (*19–21*). However, the lower liver accumulation of ^{99m}Tc-EC offered better delineation of the kidneys (*20–21*).

In conclusion, despite the limited number of subjects, this study suggests that ^{99m}Tc-EC not only has the favorable physical characteristics of ^{99m}Tc labeling and simplicity of preparation, but also it seems to have a strong potential in providing superior visual and quantitative evaluation of renal function. Clinical investigations in larger series of patients with various renal diseases are needed in order to reach a better understanding of renal handling and clearance of ^{99m}Tc-EC for routine clinical use as a measurement of renal function.

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