

Comparative scintigraphic study of renal function with ^{99m}Tc -Mercaptoacetyl-triglycine and ^{99m}Tc -Ethylenedicysteine

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ABSTRACT

Objectives: ^{99m}Tc -MAG₃ is a standard radiotracer for renal dynamic functional study. Despite its properties for clinical uses, it has numerous technical limitations. ^{99m}Tc -EC is also a tubular radiotracer for renal imaging, which has not been used worldwide. In this study, the use of ^{99m}Tc -EC and ^{99m}Tc -MAG₃ for renal functional study were compared.

Methods: Thirty five patients (20 male, 15 female; mean age of 34.63 ± 10.69 years) were entered in the study. About 10 mCi of ^{99m}Tc -EC and ^{99m}Tc -MAG₃ were administered in different days within 7 days intervals and serial images were obtained for 30 minutes. Serum creatinine and visual scintigraphic findings of all patients were within normal limits.

Results: In this study, the renal uptake of ^{99m}Tc -EC was significantly higher than ^{99m}Tc -MAG₃ (6.20% vs 4.39% of the injected dose), while the hepatic activity of ^{99m}Tc -EC was significantly lower (307 vs 439 mean pixel count, $p < 0.0001$). Also the absolute values for some other quantitative parameters such as right and left kidney transit times and ERPF were different for each radiotracer. In spite of these differences most quantitative parameters (except for right kidney transit time, liver uptake and T_{\max} of both kidneys) showed good correlations for both agents.

Conclusion: The calculated ERPF with ^{99m}Tc -EC as compared to ^{99m}Tc -MAG₃ is in closer proximity to the true values. Also the use of ^{99m}Tc -EC compared to ^{99m}Tc -MAG₃ in clinic due to simplicity of preparation, higher stability, higher renal uptake, and lower hepatobiliary activity is better. Therefore the use of ^{99m}Tc -EC as an appropriate substitute or ever preferred radiopharmaceutical for ^{99m}Tc -MAG₃ radiopharmaceutical for renal function studies is recommended.

Keywords: Renal function, ^{99m}Tc -EC, ^{99m}Tc -MAG₃

INTRODUCTION

The search for an ideal radiopharmaceutical to study renal function was started in the early 1960s (1). Over the last 10 to 15 years, several promising technetium-99m labeled renal imaging agents have been developed (1). Among the suggested radiopharmaceuticals, ^{99m}Tc -Mercaptoacetyl-triglycine (^{99m}Tc -MAG₃) is a renal tubular agent which was introduced in 1986 as an alternative for the use of ortho-iodohypuran (OIH) with similar pharmacokinetic and human renogram pattern (2-7). Despite the excellent imaging properties of ^{99m}Tc -MAG₃ due to the physical properties of ^{99m}Tc , it has several disadvantages and limitations, such as

radiopharmaceutical impurities, instability, high hepatic uptake and requirement for heating in boiling water (8).

A few years ago, ^{99m}Tc -ethylenedicysteine (^{99m}Tc -EC) was developed as a tubular agent for dynamic renal study and proposed to be an interesting substituent for ^{99m}Tc -MAG₃ (9). ^{99m}Tc -EC, a metabolite of ethylcysteinate dimer (ECD), is excreted from the kidneys by active transport mechanism, is easily labeled with ^{99m}Tc at room temperature (10) and has a renal clearance which is closer to that of OIH, (1, 11, 12). These features together with its ease of preparation make ^{99m}Tc -L,L-EC an attractive alternative to ^{99m}Tc -MAG₃

(11). It has been stated that $^{99m}\text{Tc-EC}$ has imaging qualities similar to or even better than $^{99m}\text{Tc-MAG}_3$ (13-17). The plasma protein-bound fraction of $^{99m}\text{Tc-EC}$ (30%) is significantly lower than those of $^{99m}\text{Tc-MAG}_3$ and OIH (13). Also the labelling procedure is easy, radiochemical purity is high and the complex is stable for a long time. The lower liver activity makes $^{99m}\text{Tc-EC}$ particularly attractive in patients with renal failure. Only a limited number of cases have been enrolled in a few previous studies in order to evaluate the characteristics of renal scintigraphy with $^{99m}\text{Tc-EC}$ and $^{99m}\text{Tc-MAG}_3$ in children with various renal disorders (18), normal volunteers (15) or adult patients with obstructive renal diseases (19). The value of the above radiotracers in determination of different renal functional parameters has been compared with that of OIH in a previous study (20). However, all the above studies have important limitations such as limited number of cases, non-homogeneity of the subjects under investigation and low statistical power of analyses. Despite the final conclusions of these studies that verify rather equality of $^{99m}\text{Tc-EC}$ and $^{99m}\text{Tc-MAG}_3$ in evaluation of renal function, it has been suggested that more clinical investigations are required to have a better understanding of renal measurements for routine clinical applications (15, 19-20). Also these two renal imaging agents have not been extensively and reliably evaluated for comparison of the renal functional parameters in subjects with intact renal function. The purpose of this study was to compare $^{99m}\text{Tc-EC}$ with $^{99m}\text{Tc-MAG}_3$ in the evaluation of renal function by scintigraphy in a larger number of patients.

METHODS

Patients

The study was performed from October 2004 to November 2005. The study protocol was approved by the Ethical Committee of Tehran University of Medical Sciences. The study included forty-two consecutive patients referred to nuclear medicine institute for dynamic renal imaging. Only those patients who had normal serum creatinine (0.4 -1.4 mg/dl) were entered in the study. At the first step, each patient underwent dynamic renal imaging using $^{99m}\text{Tc-MAG}_3$. Seven patients showed a significant renal dysfunction in at least one kidney who were excluded from the study. Following signing an informed consent for patients who showed no remarkable evidence of renal dysfunction (35 cases), the second step was carried

out one week later with repeated scan using $^{99m}\text{Tc-EC}$.

Radiopharmaceuticals

For $^{99m}\text{Tc-MAG}_3$ renal scintigraphy, a commercial MAG_3 kit (manufactured by AEOI, Iran) was used. MAG_3 kit was labeled with ^{99m}Tc -pertechnetate obtained from the molybdenum-technetium elution and heated for 10 minutes in boiling water. Then it was cooled down to the room temperature.

A commercial EC kit (manufactured by AEOI, Iran) was also used for $^{99m}\text{Tc-EC}$ renal scintigraphy. The labeling and quality control procedures of both kits were properly performed on the basis of the manufacturer's guidelines. Labeling efficiency was found to be greater than 90% for both agents.

Patients' preparation and image acquisition

One hour before the image acquisition, all patients were hydrated with approximately 5 ml/kg of water. Imaging was performed in a supine position. A large filed of view (LFOV) dual-head gamma-camera (ADAC, Solus) equipped with general purpose parallel-hole collimator was used. Following intravenous bolus injection of 10 mCi of radiopharmaceuticals ($^{99m}\text{Tc-EC}$ or $^{99m}\text{Tc-MAG}_3$), dynamic renal images were obtained in two phases: sixty 1-s frames and thereafter, 174 ten-second frames. Hence, each study lasted 30 minutes. A matrix size of 128×128 pixels was used with a 10% energy window of 140-keV photopeak. Time-activity curves were generated from manually drawn regions of interest (ROIs) over the kidneys and semilunar background regions adjacent to the kidneys. The background was normalized to the area of the kidney ROIs using the protocol for the ADAC gamma-camera, and the background count was subtracted from the kidney counts. The mean pixel count of the background ROIs was also calculated and compared for both radiopharmaceuticals.

Another ROI was drawn over the liver of each patient and the mean pixel count of the liver was calculated. Each syringe was also assayed in a dose calibrator (CRC 15 R, USA) before and after dose administration.

Quantitative assessment

Differential quantitative parameters including the percentage of the injected activity two minutes after injection, time to maximum uptake (T_{max}) and transit time in the left and right kidneys, as well as the mean pixel count of the liver, the mean pixel

count of the background ROIs and ERPF were calculated by Euro Casto Menu Software.

The percentage of the injected activity which is accumulated in the kidneys by the second minute after injection (Renal uptake) was estimated based on the following formula,

$$\frac{(A-C)e^{\mu X_1} + (B-C)e^{\mu X_2}}{(D-F)} \quad \text{sensitivity}$$

in which A and B are counts of the right and left kidneys at the second minute post-injection, X_1 and X_2 are depth of the right and left kidneys, respectively; C is the average background count; μ is tissue attenuation constant for gamma rays of Technetium-99m (equal to 0.12); and D and F are the counts of the radiopharmaceutical syringe before and after radiotracer injection, respectively.

For this calculation, renal depth was estimated from the body weight and height of the patients and taking the radionuclide decay and background activity.

T_{\max} which was calculated by the computer as the time to reach the peak count in the kidney ROIs. Effective renal plasma flow (ERPF) was calculated based on the Tauxe method and following formula:

Clearance of $^{99m}\text{Tc-EC}$ and $^{99m}\text{Tc-MAG}_3 = F_{\max} \cdot [1 - \exp(-k \cdot (D/C_t - V_{\text{lag}}))]$

C_t : $^{99m}\text{Tc-EC}$ and $^{99m}\text{Tc-MAG}_3$ concentration in the plasma at time t after the injection

D: Total dose of administered radioactivity

F_{\max} : The asymptotic maximum of the EC clearance value

K: Rate constant

V_{lag} : The limit of the distribution volume equal to D/minimum Concentration

ERPF was calculated based on the two-sample method (with blood sampling at 15th and 80th minute post-radiopharmaceutical injection).

Qualitative assessment

A series of images of perfusion and clearance was obtained from each patient. Three expert nuclear physicians, who were blind of the type of administered radiotracer, interpreted the image findings by consensus. Observers subjectively graded the image quality as good, fair, or poor.

Statistical analyses

The results obtained by two renal agents ($^{99m}\text{Tc-EC}$, $^{99m}\text{Tc-MAG}_3$) were compared in the same sample of patients. SPSS for Windows (Release 12.0.0) was used for statistical analysis. For each study parameter, the mean \pm SD values were calculated.

Statistical analysis was performed using Wilcoxon signed rank test to show the magnitude of difference in related quantitative variables and Chi-square test to evaluate between-group differences of qualitative variables. Also Spearman Rho correlation coefficient analysis was used to detect the relationship between quantitative parameters for two radiopharmaceuticals. A p-value less than 0.05 was accepted as significant.

RESULTS

Thirty five patients (20 male, 15 female) with a mean age of 34.63 ± 10.69 years (range: 20-54 years) were entered in the study. In visual assessment of image quality, 27 patients (77.1%) with $^{99m}\text{Tc-EC}$ vs 18 patients (51.4%) with $^{99m}\text{Tc-MAG}_3$ revealed excellent sharpness of the images while only one (2.9%) vs four (11.5%) patients showed poor quality images, respectively. The analysis of quantitative parameters (except for right kidney transit time, liver uptake and T_{\max} of both kidneys) showed good correlations for both agents (Table 1). However the absolute values for some quantitative parameters such as renal uptake (%), liver uptake, right and left kidney transit times and ERPF were different for each radiotracer (Table 1). The correlation between T_{\max} of the right and left kidney for $^{99m}\text{Tc-EC}$ ($r=0.784$, $p<0.0001$; Fig 1-A) and $^{99m}\text{Tc-MAG}_3$ ($r=0.624$, $p<0.0001$; Fig 1-B) were significant. Also the correlation between right and left kidney transit times for $^{99m}\text{Tc-EC}$ ($r=0.567$, $p<0.0001$; Fig 2-A) and $^{99m}\text{Tc-MAG}_3$ ($r=0.794$, $p<0.0001$; Fig 2-B) were significant.

DISCUSSION

In the present study, the two renal imaging agents were evaluated for comparison of the calculated renal functional parameters in normal subjects. Although other investigators have compared the pharmacokinetics and the calculated renal functional parameters of $^{99m}\text{Tc-EC}$ with those of $^{99m}\text{Tc-MAG}_3$ and OIH in various renal disorders (15-20), there are still major limitations in applied methods and number of evaluated subjects. For example in a study reported by Kabasakal et al (20), only 11 patients were included of which no more than 6 cases were evaluated by all the three radiotracers, resulting in a too small sample size to analyze any significant difference in the performed measurements. Also their evaluation was based on constant radiotracer infusion and multiple blood sampling that is too cumbersome and impractical for daily routine clinical uses. In this study the routine renal scintigraphy was applied for practical

Table 1. Comparison of $^{99m}\text{Tc-MAG}_3$ and $^{99m}\text{Tc-EC}$ for renal functional measurements, liver uptake and background activity.

Functional parameters	Type of radiotracer		Significance of difference (P-value)	Significance of correlation
	$^{99m}\text{Tc-MAG}_3$	$^{99m}\text{Tc-EC}$		
Renal uptake (%)	4.39%	6.20%	<0.0001	r= 0.689 p<0.0001
Right kidney transit time (minute) (mean±SD)	3.09 ± 0.81	3.48 ± 0.65	0.025	r= 0.235 p= 0.174 NS*
Left kidney transit time (minute) (mean±SD)	2.93 ± 0.64	3.22 ± 0.73	0.011	r= 0.596 p<0.0001
T _{max} of the right kidney (minute) (mean±SD)	3.50 ± 0.95	3.77 ± 1.13	0.371 NS*	r=0.277 p=0.107 NS*
T _{max} of the left kidney (minute) (mean±SD)	3.60 ± 0.91	3.71 ± 0.87	0.446 NS*	r=0.780 p=0.049
Mean hepatic activity (Mean count/pixel)	439 ± 118	307 ± 73	<0.0001	r=0.461 p=0.005
Mean renal background activity (Mean count/pixel)	108 ± 26	108 ± 42	0.636 NS*	r=0.708 p<0.0001
Calculated Mean ERPF	212.11 ± 80.25	288.31 ± 90.62	<0.0001	r=0.702 p<0.0001

*Not significant

assessment of renal functional parameters and, significant difference was observed between renal uptakes of the two radiotracers with obvious superiority of $^{99m}\text{Tc-EC}$. The transit times for right and left kidneys which were calculated on the basis of $^{99m}\text{Tc-MAG}_3$ were slightly lower than that of $^{99m}\text{Tc-EC}$. In spite of these statistical differences, they have no important effect on clinical impact of the test. In addition, the study shows relatively good correlation between left kidney transit times calculated by $^{99m}\text{Tc-EC}$ and $^{99m}\text{Tc-MAG}_3$, while the correlation between right kidney transit times using each of two radiotracers was poor. This fact as well as the greater variance of right kidney transit time calculated by $^{99m}\text{Tc-MAG}_3$ as compared with $^{99m}\text{Tc-EC}$ may result from higher hepatic uptake of the former radiopharmaceutical which can potentially interfere with quantitative parameters of the right kidney. On the other hand, there was no significant differences in some quantitative functional variables of these radiotracers including T_{max} of both kidneys, and mean renal background activity. This fact along with lower hepatic activity

of $^{99m}\text{Tc-EC}$ makes this radiopharmaceutical more suitable and reliable for renal imaging and especially for differential assessment of the right kidney. This conclusion is confirmed by the results of qualitative analysis, in which the blind observers found that $^{99m}\text{Tc-EC}$ provides images of better quality and excellent delineation of the kidneys. This finding has also been previously established in another study (13).

Also the ERPF calculated based on $^{99m}\text{Tc-EC}$ study (288.31 ml/min) was higher than that obtained by $^{99m}\text{Tc-MAG}_3$ (212.11 ml/min) and in fact the calculated ERPF with $^{99m}\text{Tc-EC}$ is in closer proximity to the true values in comparison to $^{99m}\text{Tc-MAG}_3$. Some other studies have shown similar results (1, 15, 16, 20), possibly indicating that $^{99m}\text{Tc-EC}$ clearance can be used as a better parameter of kidney function and as a more precise estimation of ERPF. In a study reported by Ozker et al, T_{max} and T_{1/2} have been assessed in 16 patients with obstructive renal disease using these two radiotracers (19). As it was expected, in the above study the absolute value of T_{max} in patients with

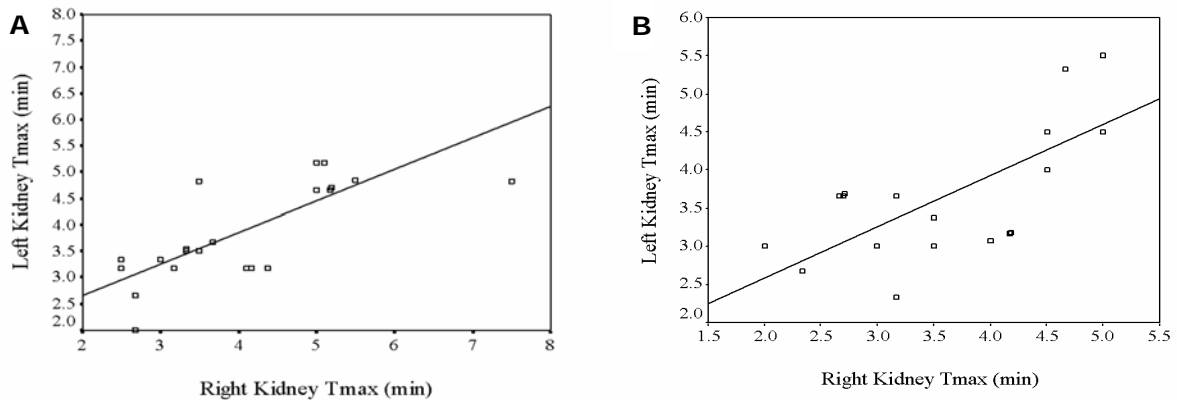


Figure 1. Correlation between T_{\max} of the right and left kidneys calculated for $^{99m}\text{Tc-EC}$ (A) and $^{99m}\text{Tc-MAG}_3$ (B).

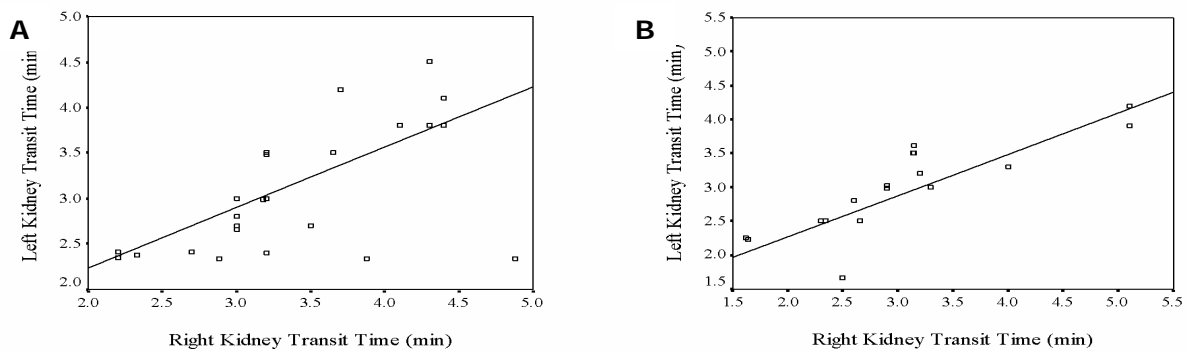


Figure 2. Correlation between right and left kidney transit times calculated for $^{99m}\text{Tc-EC}$ (A) and $^{99m}\text{Tc-MAG}_3$ (B).

obstructive renal disease is much higher than those of this study, while the values for control cases are the same as near-normal patients of this investigation. In agreement with the results of this study, no significant difference has been observed between T_{\max} values of the two radiotracers even in patients with impaired renal function.

Moreover, clinical usage of $^{99m}\text{Tc-EC}$ is much easier than $^{99m}\text{Tc-MAG}_3$ because of its better properties such as simplicity of preparation, higher stability, lack of boiling requirement and convenient labeling at room temperature (14). According to the previous reports, the use of $^{99m}\text{Tc-EC}$ consistently resulted in a high quality product, and the labeled kit was proved to have a shelf-life of at least 8 hours (14). Hence, in our opinion, these labeling conditions make $^{99m}\text{Tc-EC}$ an ideal and reliable agent with special advantages over $^{99m}\text{Tc-MAG}_3$.

The results of previous animal (14-15) and preliminary human studies in normal volunteers (15) obtained with HPLC-purified $^{99m}\text{Tc-EC}$ confirm the results of this study. These data have

shown good functional correlation in both $^{99m}\text{Tc-EC}$ and $^{99m}\text{Tc-MAG}_3$, but the pharmacokinetics behavior of $^{99m}\text{Tc-EC}$ has been shown to be closer to OIH (15). It was also found that the renal uptake of $^{99m}\text{Tc-EC}$ was significantly higher than $^{99m}\text{Tc-MAG}_3$. This difference could be explained by the previous findings of Eshima et al (17), who have reported the higher protein binding of $^{99m}\text{Tc-MAG}_3$ as compared to $^{99m}\text{Tc-EC}$. Results of this study confirmed the conclusion of Kibar et al, who stated that $^{99m}\text{Tc-EC}$ has excellent imaging characteristics, and even has some advantages over $^{99m}\text{Tc-MAG}_3$ (18). They also suggest that this agent can be used routinely, which is similar to our conclusion. Findings of this study are also in concordance with those of Prvulovich et al (11), who suggested $^{99m}\text{Tc-EC}$ as an attractive alternative to $^{99m}\text{Tc-MAG}_3$, even in patients with chronic renal failure.

Finally from dosimetric point of view, as it has been reported (21), the effective dose to the patient for unit activity of $^{99m}\text{Tc-EC}$ is comparable to other ^{99m}Tc labeled radiopharmaceuticals (21).

CONCLUSION

From the results of this study it is suggested that ^{99m}Tc -EC can be used routinely as an interesting substitute at for ^{99m}Tc -MAG₃. The calculated ERPF with ^{99m}Tc -EC is in closer proximity to the true values as compared to the ^{99m}Tc -MAG₃. Also clinical usage of ^{99m}Tc -EC is easier than ^{99m}Tc -

MAG₃ because of better properties such as simplicity of preparation, higher stability, higher renal uptake, and less hepatobiliary activity.

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