Simplified Technetium-99m-EC Clearance in Adults from a Single Plasma Sample

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Technetium-99m-EC has recently been introduced as an alternative renal tubular agent to ^{131}I-ortho iodohippurate (OIH). It has been shown that ^{99m}Tc-EC clearance shows strong correlation with OIH clearance and it is possible to estimate effective renal plasma flow. In routine clinical studies, it is practical to use one or two plasma sample methods instead of multiple plasma samples for clearance determination. An attempt was made to determine ^{99m}Tc-EC clearance with one sample method. **Methods:** Data from 72 subjects were collected. To increase the range of renal function, two anuric hemodialysis patients were also included. Clearances were determined by the open two-compartment model. **Results:** The clearance range was 12 ml/min to 660 ml/min with a mean of 275 ± 117 ml/min. Analysis of correlation was made by Tauxe's method. The least standard error of estimation (s.e.e. = 32.71 ml/min) and the best correlation (r = 0.97) between the theoretical volume distribution and the clearance estimations were obtained from the 54-min plasma sample. **Conclusion:** This study suggests that EC clearance could be determined by a simplified single-sample method with an acceptable s.e.e.

Key Words: technetium-99m-ethylenedicisteine; clearance determination; radionuclide renography; effective renal plasma flow; renal function

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Technetium-99m-ethylenedicisteine (^{99m}Tc-EC) is a new renal tubular agent introduced as a substitute for ^{131}I-orthoiodohippurate (OIH) (*1*). Human studies of ^{99m}Tc-EC showed considerable promise as a ^{99m}Tc replacement for ^{131}I-OIH (*2–5*). It has been demonstrated that the pharmacokinetics of ^{99m}Tc-EC in determination of effective renal plasma flow is better than those of ^{99m}Tc-mercaptoacetyltriglicine (^{99m}Tc-MAG3), and renal extraction efficiency is higher, with a value of 70% (*1–7*). High-quality images, low liver retention and ease of preparation at room temperature with high labeling efficiency are the other advantages of ^{99m}Tc-EC over ^{99m}Tc-MAG3 (*2–7*).

The quantitative renal function with renal radiolabeled agents is widely used. However, the multiple-sample method is not practical for quantitative routine renal function determination. To overcome this limitation, one or two plasma sample methods have been used as simple and accurate procedures for routine clinical use (*8,9*). This study was performed to develop a simplified single plasma sample method for estimation of ^{99m}Tc-EC plasma clearance.

MATERIALS AND METHODS

Seventy-two subjects (41 men, 31 women; age range 17–59 yr) participated in this study; 58 had various degrees of renal impairment, including 8 transplant patients. All subjects had been referred to our department for routine kidney function evaluation. To increase the range of renal function, 2 anuric hemodialysis patients and 14 normal subjects were also included in the study. The study protocol was approved by the Medical Faculty Ethical Committee.

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Subjects were injected with 200 MBq ^{99m}Tc-EC when scintigraphy was performed and 5 MBq ^{99m}Tc-EC when scintigraphy was not performed. Injection was through a three-way stopcock connected to an intravenous catheter and then flushed with saline. Subsequently, 11 blood samples were obtained from 26 subjects, and 7 blood samples were obtained from 44 subjects for a period of 60 min. Anuric patients were studied for 180 min, and 16 blood samples were obtained from them. Blood samples were centrifuged, 0.2-ml plasma samples were weighed and plasma radioactivity (C) was determined by counting the samples in a well-scintillation gamma counter. The injected dose (ID) was estimated from the weight difference of syringes before and after the injection and from a standard activity that was prepared at the time of injection and diluted in 100 ml to 250 ml saline. The data were plotted against time and rate constants (α and β), and the intercepts (A and B) for slow and fast components were calculated by using the bi-exponential curve fit analysis. An open two-compartment model suggested by Sapirstein et al. (10) was used for plasma clearance determination. The theoretical volume distribution (ID/C_t), for 1-min intervals up to 95 min, was calculated by using the formula:

$$C_t = A\, e^{-\alpha t} + B\, e^{-\beta t}. \qquad \text{Eq. 1}$$

An exponential fit, in the form of the formula suggested by Tauxe et al. (*8*), was carried out for estimation of clearance from calculated theoretical volume distributions as follows:

$$F = F_{max}[1 - \exp(-\alpha((ID/C_t) - V_{lag}))], \qquad \text{Eq. 2}$$

where F is the clearance, F_{max} is an asymptotic maximal value of ^{99m}Tc-EC clearance, α is the rate constant slope and V_{lag} is the intercept of the fitted curve on the abscissa derived iteratively by the Gauss-Newton method.

Statistical analysis was performed by conventional regression analysis ($p < 0.05$, 95% confidence intervals).

RESULTS

Seven or more plasma samples of ^{99m}Tc-EC clearance ranged from 12 ml/min to 660 ml/min with a mean value of 275.5 ± 117.4 ml/min. The mean clearance range for the normals was 392.8 ± 118.3 ml/min. Figure 1 depicts the s.e.e. against various sampling times). From these data it can be seen that the nadir of the s.e.e. is between 50 and 60 min. The least s.e.e. of ^{99m}Tc-EC clearance from theoretical volume distributions (s.e.e. = 32.71 ml/min, r = 0.97, $p < 0.001$) was obtained from the 54-min plasma sample. The equation best fitting our data is

$$Cl_{EC} = 1454.21[1 - \exp(-0.00457((ID/C_{54}) - 3.55))]. \qquad \text{Eq. 3}$$

The parameters of the equation for various sampling times are presented in Tables 1 and 2.

DISCUSSION

In adults, several algorithms are available that allow estimation of the renal clearances of ^{99m}Tc-MAG3 and OIH by means of one blood sample that is obtained at 43 and 44 min after

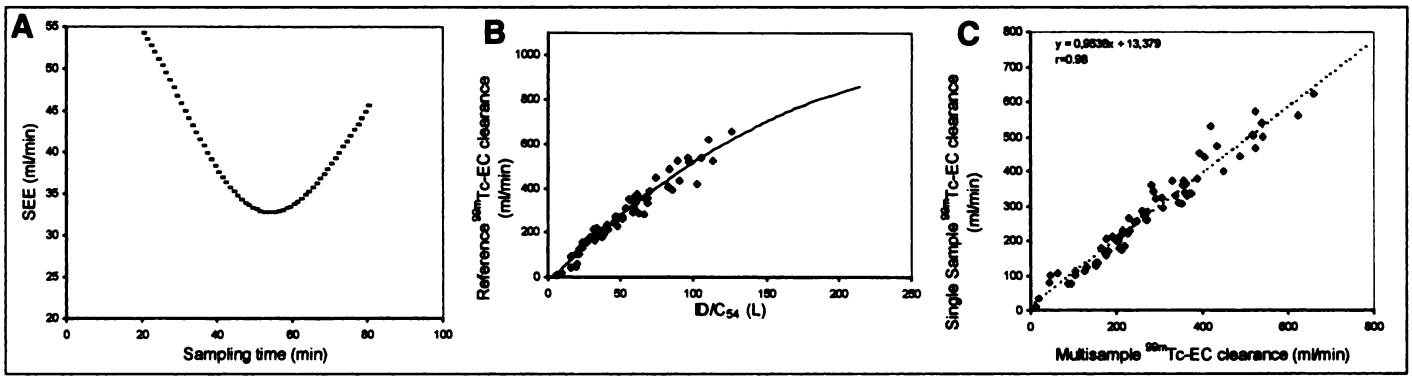

FIGURE 1. (A) Plots of s.e.e. ^{99m}Tc-EC clearance and theoretical volume distributions obtained from various sampling times. The least s.e.e. was obtained at 54 min. (B) Technetium-99m-EC clearance as measured by multiple plasma sample method (ordinate) and theoretical volume of distribution (ID/C_{54}) at 54 min (abscissa). (C) Correlation of clearances between single-sample ^{99m}Tc-EC clearance obtained from 54-min plasma sample (abscissa) and reference ^{99m}Tc-EC clearances (ordinate) (y = 13.379 + 0.9538x; r = 0.98).

injection, respectively (*8,9*). Similarly, results of this study suggest that ^{99m}Tc-EC clearance can be estimated from a single plasma sample with an acceptable error of estimation for routine clinical studies (s.e.e. 32.7 ml/min). The optimal sampling time is found to be 54 min postinjection. The difference in optimal sampling times between ^{99m}Tc-EC and the other tubular agents may be explained by the lower rate constants of ^{99m}Tc-EC compared to those of ^{99m}Tc-MAG3 and OIH (*1,2,5,7*).

The method based on the regression between a reference clearance and the plasma concentration is population dependent, and the technique is feasible when a patient has the same characteristics as the group of patients that the method is derived from. The sampling time for the validity of the single-sample technique is a function of distribution volume and the clearance and varies with every case rather than being a constant time (*11,12*). Accordingly, with a different patient population, Stoffel et al. (*13*) reported a different optimal sampling time for ^{99m}Tc-EC (i.e., 80 min after injection). The sampling time for single plasma sample clearance determinations depends on the level of renal function. Low- and high-clearance rates require different plasma sampling times (*12*). Plasma samples can be obtained closer to the time of injection when the renal function is good, and longer times are required when the renal function is poor. The optimal sampling time is preferred when the renal function is not known. This study was conducted in 72 patients with a wide range of renal function.

TABLE 1
Values of Coefficients of the Exponential Formula and Standard Error of Estimations of Regression

Time (min)	F_{max} (ml/min)	α (liter^{-1})	V_{lag} (liter)	S.e.e (ml/min)	Corr. Coef. (r)
50	1476.03	0.0050	4.1265	33.07	0.974
51	1476.10	0.0048	3.9806	32.90	0.974
52	1472.48	0.0048	3.8352	32.78	0.975
53	1465.27	0.0046	3.6908	32.72	0.975
54	1554.21	0.0046	3.5499	32.71	0.975
55	1439.40	0.0045	3.4113	32.75	0.975
56	1421.07	0.0045	3.2802	32.84	0.975
57	1399.39	0.0045	3.1554	32.98	0.974
58	1374.90	0.0045	3.0387	33.18	0.974
59	1347.92	0.0045	2.9316	33.42	0.974
60	1318.96	0.0045	2.8316	33.70	0.973

Volume distributions were obtained between 50-min to 60-min plasma samples.

TABLE 2
Values of Coefficients of the Exponential Formula and Standard Error of Estimations of Regression

Time (min)	F_{max} (ml/min)	α (liter^{-1})	V_{lag} (liter)	S.e.e (ml/min)	Corr. Coef. (r)
30	1129.74	0.0115	6.1750	45.66	0.950
35	1193.08	0.0094	6.0519	41.38	0.959
40	1267.37	0.0077	5.7457	37.62	0.966
45	1432.17	0.0058	4.8182	34.75	0.971
65	1161.39	0.0047	2.4818	35.61	0.970
70	1015.71	0.0050	2.3350	38.10	0.966
75	901.17	0.0053	2.2762	40.84	0.960
80	816.56	0.0055	2.1766	43.62	0.955
85	755.10	0.0057	1.9444	46.34	0.949

Volume distributions were obtained between 35-min to 45-min and between and 65-min to 85-min plasma samples.

The clearance of ^{99m}Tc-EC ranged between 12 ml/min and 660 ml/min with a mean value of 275.5 ± 117.4 ml/min. The optimal sampling time of 54 min can be used in patients for whom the renal function is not known.

CONCLUSION

This study presents a simplified single-sample method for determination of ^{99m}Tc-EC clearance. Since the s.e.e. is not different, the 50-min sampling time can be also used for practical purposes (Table 1). The s.e.e., with this formula, seems to be within an acceptable range for most clinical studies. This finding needs to be validated by a prospective study, preferably with a continuous infusion ^{99m}Tc-EC clearance determination.

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REFERENCES

1. Verbruggen AM, Nosco DL, Nerom VCG, Bormans GM, Adrians PJ, De Roo MJ. Technetium-99m-L,L-ethylenedicysteine: a renal imaging agent. I. Labeling and evaluation in animals. *J Nucl Med* 1993;20:738–746.
2. Van Nerom CG, Bormans GM, De Roo MJ, Verbruggen AM. First experience in healthy volunteers with technetium-99m-L,L-ethylenedicysteine, a new renal imaging agent. *Eur J Nucl Med* 1993;20:738–756.
3. Özker K, Önsel Ç, Kabasakal L, et al. A new technetium labeled renal agent Tc-99m-ethylenedicysteine: a comparative renal scintigraphic study with Tc-99m-

MAG3 and I-131-OIH in patients with obstructive renal diseases. *J Nucl Med* 1994;35:840–845.
4. Kabasakal L, Turoğlu HT, Önsel Ç, et al. Comparative continuous infusion renal clearance of Tc-99m-EC, Tc-99m-MAG3 and I-131-OIH. *J Nucl Med* 1995;36:224–228.
5. Kabasakal L, Atay S, Vural AV, et al. Evaluation of technetium-99m-ethylenedicysteine in renal disorders and determination of extraction ratio. *J Nucl Med* 1995;36:1398–1403.
6. Kabasakal L, Özker K, Işıtman AT, Önsel Ç. Relationship between the OIH and Tc-99m-EC clearances. *Nucl Med Commun* 1994;15:1006–1007.
7. Surma MJ, Wiewiora J, Liniecki J. Usefulness of Tc-99m-N,N-ethylene-l-dicysteine complex for dynamic kidney investigations. *Nucl Med Commun* 1994;15:628–635.
8. Tauxe WN, Dubovsky E, Kidd T, Diaz F, Smith LR. New formulas for the calculation of effective renal plasma flow. *Eur J Nucl Med* 1982;7:51–54.
9. Russel CD, Taylor A, Eshima D. Estimation of technetium-99m-MAG3 plasma clearance in adults from one or two blood samples. *J Nucl Med* 1989;30:1955–1959.
10. Sapirstein LA, Vidt D, Mandel M, et al. Volumes of distribution and clearances of intravenously injected creatinine in the dog. *Am J Physiol* 1955;181:330–336.
11. Chatterton BE. Limitations of the single sample tracer method for determining glomerulat filtration rate. *Br J Radiol* 1978;51:981–985.
12. Kotzerke J, Burchert W, Wiese H, Smekal UV, Hundeshagen H. Limitations of clearance determination using the single sample distribution volume method. *Eur J Nucl Med* 1992;19:19–24.
13. Stoffel M, Jamar F, Van Nerom C, et al. Technetium-99m-L,L-ethylenedicysteine clearance and correlation with iodine-125-orthoiodohippurate for the determination of effective renal plasma flow. *Eur J Nucl Med* 1996;23:365–370.

Technetium-99m-Tetrofosmin Uptake in Sarcoidosis Stage I

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The uptake of ^{99m}Tc-tetrofosmin in enlarged lymph nodes, of the lung hilus, in the case of sarcoidosis Stage I (histopathologically confirmed by mediastinoscopic biopsy) is demonstrated. On a routine chest radiograph of a 78-yr-old woman, hilar lymphadenopathy was first detected. In the following mammography, disseminated micro calcifications were found in the left breast and a ^{99m}Tc-tetrofosmin study was performed for detection of breast cancer. Scintigraphy using ^{99m}Tc-tetrofosmin showed clear uptake in the hilar lymph nodes, but not in the left breast. The ^{99m}Tc-tetrofosmin uptake in the hilar lymph nodes was due to sarcoidosis confirmed by histology. Therefore, ^{99m}Tc-tetrofosmin scintigraphy may be useful in patients with suspected sarcoidosis, especially in Stage I.

Key Words: technetium-99m-tetrofosmin; hilar lymphadenopathy; sarcoidosis Stage I; SPECT

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Sarcoidosis is a chronic inflammatory multisystem disease of uncertain etiology. The diagnosis of pulmonary sarcoidosis is often established by exclusion. It is difficult to assess the activity of sarcoidosis by conventional clinical, radiological and physiological parameters as none of these are specific for the inflammatory process. Gallium-67 scintigraphy is effective in the detection of lesions not revealed by conventional methods of investigation, particulary those affecting mediastinum (*1–3*). Technetium-99m-tetrofosmin is a lipophilic, cationic complex proposed for myocardial perfusion imaging. It has been found that ^{99m}Tc-tetrofosmin also has other useful applications especially in oncology. Recent articles were able to demonstrate its uptake in parathyroid adenomas (*4*), recurrence and distant metastases of differentiated thyroid cancer (*5–7*) as well as in malignant breast tumors (*8–10*).

We report a case of positive ^{99m}Tc-tetrofosmin uptake in hilar lymphadenopathy in a case of sarcoidosis Stage I.

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CASE REPORT

In a 78-yr-old woman, who underwent a routine check-up, a chest radiograph was taken and hilar adenopathy was first detected. The subsequently performed mammography showed a region (about 15 mm in diameter) with disseminated microcalcifications in the left breast. To reveal possible breast cancer, a ^{99m}Tc-tetrofosmin study was performed. For imaging, we used a double-headed gamma camera with LEHR collimators. Five minutes after intravenous injection of 370 MBq ^{99m}Tc-tetrofosmin, three static images were taken in prone position (right lateral, left lateral and anterior), followed by SPECT and three-dimensional reconstruction 20 min postinjection. All images showed an increased uptake in the mediastinal cavity (Fig. 1). In the region of the left breast, no pathological uptake could be detected. Because of these findings, the patient underwent MRI of the chest and mediastinum. The images showed a conglomerate of partially, but distinctly enlarged, mediastinal and hilar lymph nodes (Fig. 2). Other investigations, including laboratory findings (full blood count, angiotensin-converting enzyme, tumor markers, lymph cell typing), spirometry, ECG, sonography of the neck and the abdomen, transmission CT of the abdomen and bone marrow biopsy were all reported to be normal. Subsequent mediastinoscopy with lymph node biopsy was performed. Pertaining to histology, the diagnosis sarcoidosis was confirmed (Fig. 3).

DISCUSSION

Sarcoidosis is a systemic granulomatous disease of unknown etiology. Uptake for ^{67}Ga and J001 macrophage targeting glycolipopeptide has been previously described in sarcoidosis by various authors (*2,3,11*). In addition, only a few case reports on ^{201}Tl and ^{99m}Tc-sestamibi for imaging sarcoidosis are found in the literature (*12,13*). One article describes the uptake of ^{99m}Tc-tetrofosmin in lung tumors (*14*), but not in sarcoidosis (neither Stage I nor other stages). Technetium-99m-labeled tetrofosmin is a cationic, lipophilic radiopharmaceutical proposed for myocardial imaging. The mechanism by which it concentrates in tumor tissue was recently described by Arbab et al. (*15*). In our case, the images showed that capture of the tracer by the enlarged hilar lymph nodes was quite satisfactory, and it left the area of the