Technetium-99m ECD: A New Brain Imaging Agent: In Vivo Kinetics and Biodistribution Studies in Normal Human Subjects

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Lipophilic neutral ^{99m}Tc complexes of diaminedithiol (DADT) ligands cross the brain-blood barrier. A new derivative of DADT family, ^{99m}Tc ethyl cysteinate dimer (ECD) showed high brain uptake in nonhuman primates. We report here the in vivo kinetics and biodistribution results in 16 normal human subjects. Dynamic images of brain obtained for 10 min following an i.v. administration of [^{99m}Tc]ECD showed that the maximum ^{99m}Tc brain activity reached within 1 min and remained near that level for the next 10 min. The blood clearance of the tracer was very rapid and the activity remaining in blood after 5 min was <10%. Within 2 hr 50% of ^{99m}Tc activity was excreted in urine. Anterior and posterior total-body images were obtained at 5, 30, 60 min, 2, 4, 24, and 48 hr using a moving table at 20 cm/min. Percent injected dose was calculated for different organs and tissues. The brain uptake was 6.5 ± 1.9% at 5 min postinjection and remained relatively constant over several hours. Two-compartment analysis of brain time-activity curve showed that 40% of brain activity washed out faster ($T_{1/2}$ = 1.3 hr) while the remaining 60% had a slower clearance rate ($T_{1/2}$ = 42.3 hr). Some of the tracer was excreted through the hepatobiliary system. Lung uptake and retention of [^{99m}Tc]ECD was negligible. Radiation dosimetry is favorable for the administration of up to 20–40 mCi of [^{99m}Tc]ECD. These results show that [^{99m}Tc]ECD is rapidly extracted and retained by the brain providing favorable conditions for single photon emission computed tomography imaging.

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Evaluation of cerebral perfusion using single photon emission computed tomography (SPECT) is evolving into a useful diagnostic technique in patients with a variety of disorders affecting the central nervous system (*1*). A number of neutral, lipophilic radiotracers have been developed. These complexes cross intact blood-brain barrier (BBB) and are trapped within the brain parenchyma. While the radioiodinated mono- and diamines, iodine-123 N-isopropyl p-iodoamphetamine ([^{123}I]IMP) and ^{123}I N,N,N′-trimethyl-N′-[2-hydroxyl-3-methyl-5-iodobenzyl]-1,3 propanediamine (HIPDM) were the first to be evaluated (*2*), a technetium-99m (^{99m}Tc) tracer would be more convenient and desirable.

Two types of ligands, propyleneamine oxime (PnAO) and diamine dithiol (DADT) or bis-aminoethane thiol (BAT) have been shown to form neutral ^{99m}Tc complexes. Volkert et al. (*3*), in 1984, described [^{99m}Tc] PnAO as a tracer for regional cerebral blood flow measurement (rCBF). The washout rate of this agent, however, was too rapid for SPECT imaging. Subsequently, various analogs of PnAO were evaluated. Among these, ^{99m}Tc-d,l-HM-PAO (*4*) has the most favorable prop-

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erties for brain SPECT imaging, and was recently approved for cinical use in the United States.

Kung et al. (*5*), in 1984, synthesized three derivatives of the BAT ring. The ^{99m}Tc complexes of these ligands had a significant brain uptake but were not retained. Lever et al. (*6*), in 1985, developed a new analog of the DADT group called ^{99m}Tc-N-piperidinylethyl-DADT that showed rapid uptake and prolonged retention in the brain of primates. Recently, Cheesman et al. (*7*) developed a number of ^{99m}Tc complexes of ester derivatized DADT ligands. Of these compounds. ^{99m}Tc N,N'-1,2-ethylenediylbis-L-cysteine diethyl ester (ECD) showed excellent uptake and retention characteristics for SPECT imaging in primates (*8*) and therefore, was chosen for clinical evaluation. We report the initial biodistribution and kinetic studies of [^{99m}Tc]ECD in normal human subjects (*9*).

MATERIALS AND METHODS

Radiopharmaceutical

The kit for the preparation of [^{99m}Tc]ECD was supplied by Dupont Inc. ECD was labeled with 25 mCi of [^{99m}Tc] pertechnetate. The labeling efficiency was tested by thin layer chromatography using Whatman RP-C18 glass plates and eluted with a solvent system containing 60% acetone and 40% ammonium acetate (0.5*M*, pH 4.0). The radioactivity on the plates was quantitated by gamma camera imaging.

Human Subjects

The study population consisted of 16 normal human subjects (13 male, 22–49 yr of age and three females, 22–54 yr of age; overall mean 31.1 ± 9.4 yr) with no medical history of cerebral vascular disease, mental disorder, CNS disorders, hypertension, endocrine or cardiac disease. The subjects were asked not to take any medication 72 hr prior to the study and to fast for 4 hr prior to the study. Written informed consent approved by our institutional IRB was obtained from each volunteer.

Pharmacokinetic Studies

Each subject was injected with 10 mCi of [^{99m}Tc]ECD intravenously followed by a 10-ml saline flush. Blood samples were collected at 1, 2, 3, 4, 5, 10, 15, 30, 60 min, 4 and 24 hr from the contralateral arm. After the injection of tracer, the subjects were asked to collect urine in four separate containers between 0–2, 2–4, 4–6, and 6–24 hr and feces were individually collected for 48 hr. Radioactivity in whole blood and urine samples was counted along with an aliquot of the standard (the radiotracer was appropriately diluted) in a well counter. The activity in feces and an appropriate standard was counted using a gamma camera without a collimator. The percent ^{99m}Tc activity in the total blood was calculated using the normal blood volume that was estimated based on height and weight (*10*). The ^{99m}Tc activity in urine and feces was also expressed as a percentage of total injected radioactivity.

Imaging Protocol and Biodistribution Studies

To assess dynamic changes in the biodistribution of [^{99m}Tc] ECD, serial whole-body images were obtained with a large field gamma camera (Omega–500 Technicare, Solon, OH) and a GAP parallel hole collimator. In order to relate images to each other, all imaging was performed at a uniform pre-set speed of 20 cm/min. A matrix size of 256 × 256 was used to record all information in digital format. Anterior and posterior total-body images starting at 5 min postinjection were acquired. Subsequently, similar imaging studies were performed at 0.5, 1, 2, 4, 24, and 48 hr.

The total-body counts in the anterior and posterior views for each time point were calculated by taking a region of interest (ROI) encompassing the entire body. Specific ROIs were drawn for brain, thyroid, heart, lungs, liver, kidney, gall bladder, urinary bladder, and legs (both legs included). For the organs that overlapped, a different technique was used to calculate the uncontaminated counts. In addition to the ROI of the entire organ, a small ROI was drawn in an area of the organ uncontaminated by an overlapping organ. The counts/pixel in this small region were taken as representative of the entire organ and the total organ counts were then extrapolated based on the relative sizes of the two regions. This technique was used for liver, lung, kidney, and gallbladder. When the size of an organ was once defined by an ROI (number of pixels = A), it was then used on all the images at each of the time points and projections. The ROI for the colon was drawn only for the images acquired at 4 and 24 hr. To determine the background, ROI was drawn in proximity to the organ of interest and average counts/pixel in the background (B) were calculated. The net counts in an organ are obtained by subtracting the background counts (A X B). For total body, brain and legs, an area along the body contour was chosen as background. The net counts in ROIs for different organs in both anterior and posterior views were calculated for each acquisition. The geometric mean of counts in an ROI at different times postinjection were calculated and normalized to the beginning of the first study (5 min postinjection). The percent injected dose in each organ was calculated by dividing the decay corrected geometric mean of organ or corresponding ROI counts by the geometric mean of total-body counts at 5 min postinjection.

In order to study the initial kinetics of [^{99m}Tc]ECD brain uptake, serial dynamic images (5 sec/frame) of the head in an anterior position were obtained in one of the subjects for the first 10 min after the i.v. injection of [^{99m}Tc]ECD. The images were recorded in a 64 × 64 matrix and stored in an imaging computer (Microdelta, CDA). Whole brain ROI was selected to generate the time-activity curve.

RESULTS

The labeling efficiency of [^{99m}Tc]ECD kit was consistently very high (96 ± 2%). The average amount of ^{99m}Tc activity injected in the 16 normal subjects was 9.6 ± 0.8 mCi. Each subject was injected within 30 min after tracer preparation.

Figure 1B shows the time-activity curve of [^{99m}Tc] ECD in the brain of the normal human subject in whom the initial 10 min dynamic study was performed. Technetium-99m activity in the brain reached a maximum at 1 min after the injection and remained near that level for the next 10 min. Anterior and right lateral

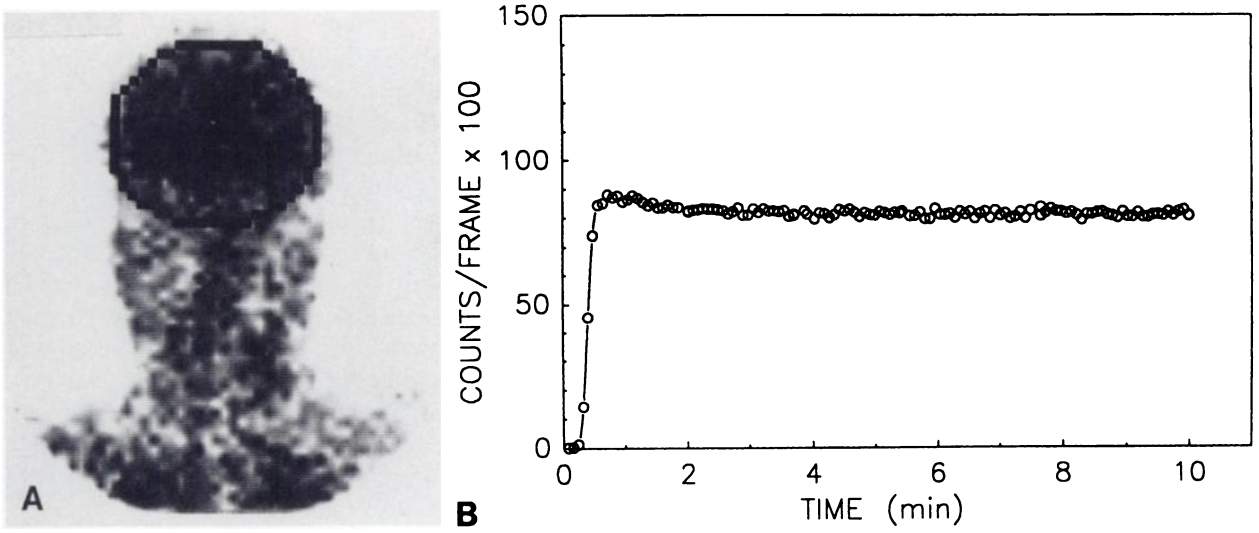

FIGURE 1
The kinetics of [^{99m}Tc]ECD in normal brain. Serial dynamic images were obtained for 10 min (5 sec/frame). The ROI was created to include the whole brain (A), and the time-activity curve (B) shows the brain uptake and retention of ^{99m}Tc activity.

planar static images (Fig. 2) taken 1.5 hr postinjection clearly show intense uptake of [^{99m}Tc]ECD in the brain.

Blood clearance of [^{99m}Tc]ECD is shown in Figure 3. The initial activity in blood at 1 min was 19 ± 22% that quickly decreased to ~10% by 5 min and remained relatively constant for the next 10 min. The amount of activity in the blood at 4 hr was 1.0 ± 0.4% of the injected activity.

The amount of ^{99m}Tc activity excreted in the urine (Table 1) within the first 2 hr was 50 ± 13%. Over the next 4 hr, an additional 19% of ^{99m}Tc activity was excreted in the urine. Total amount of ^{99m}Tc activity excreted in urine within a 24-hr period was 74%.

The whole-body images of [^{99m}Tc]ECD in vivo distribution at various times (5 min, 1, 2, and 4 hr) postinjection are shown in Figure 4. The quantitative data describing the kinetics of organ uptake and clearance are summarized in Table 2. The brain uptake of [^{99m}Tc]ECD at 5 min was 6.5 ± 1.9% which decreased to 5.2 ± 1.3% by 1 hr. Over the next 3 hr, only 27% of ^{99m}Tc activity washed out of the brain.

Lung uptake and retention of [^{99m}Tc]ECD was negligible. The initial uptake was 4.7 ± 2.8% at 5 min which dropped to <1% by 2 hr. At 5 min, the amount of ^{99m}Tc activity in legs was 8.5 ± 4.1% which dropped to 1.3 ± 0.6% by 4 hr. Technetium-99m-ECD was excreted primarily by the kidneys. The total-body activity at 4 hr was 28% of the initial 5 min activity. This

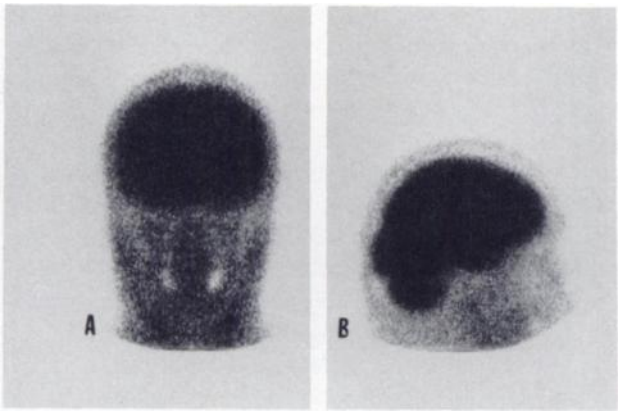

FIGURE 2
Static planar images of [^{99m}Tc]ECD brain activity 1.5 hr after the injection of the tracer. (A) anterior and (B) right lateral.

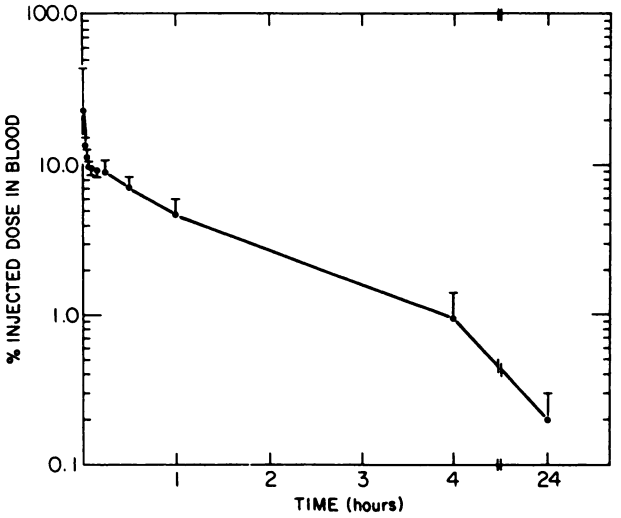

FIGURE 3
Clearance of [^{99m}Tc]ECD from blood. The ^{99m}Tc activity in the whole blood (total volume) was expressed as a percentage of total injected activity.

TABLE 1
Percent Technetium-99m Activity in Urine Collected and Retained in Body Following Intravenous Administration of [^{99m}Tc]ECD

Time (hr)	Urine collected	Time (hr)	Urine retained
		0	88.8*
0–2	50.2 ± 13.0	2	38.6
2–4	14.8 ± 8.1	4	23.8
4–6	4.2 ± 2.1	6	19.6
6–24	4.8 ± 3.0	24	14.9

*Since the total-body feces collection was 11.2 ± 6.2%, the activity retained in the urine at time zero was assumed to be 88.8%.

significant decrease in total-body activity was well correlated with the amount of activity (65%) excreted in the urine within 4 hr.

Some of the tracer was excreted through the hepatobiliary system. The initial liver uptake of the tracer was 17 ± 7% at 5 min which decreased to 2.5 ± 1.2% by 4 hr. The activity in gallbladder was prominent even at 4 hr (Fig. 4). The ^{99m}Tc activity excreted in the 48-hr feces collection was 11.2 ± 6.2% which includes the colon activity seen in 48-hr images.

Radiation dosimetry was calculated for [^{99m}Tc]ECD using the MIRD 11 Scheme (*11*). In order to calculate the residence times in different organs the following assumptions were made based on the biodistribution data described above.

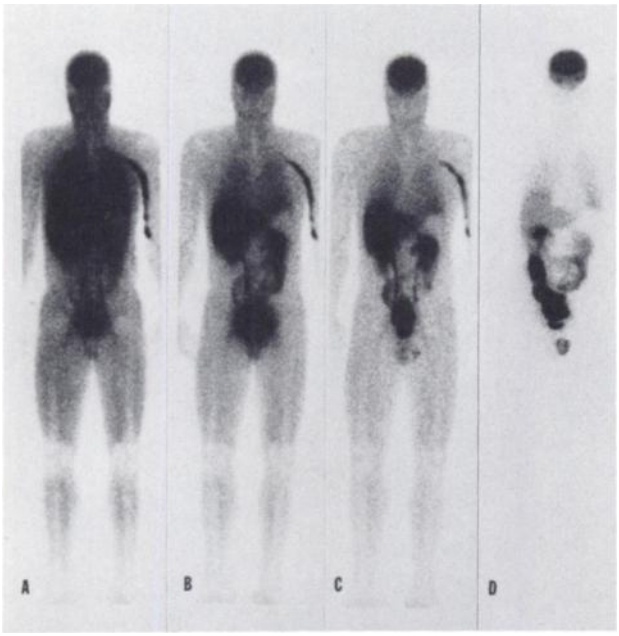

FIGURE 4
Total-body images of [^{99m}Tc]ECD distribution in a normal human subject. Anterior views were obtained at (A) 5 min, (B) 1 hr, (C) 2 hr, and (D) 4 hr.

1. Instantaneous uptake in brain, liver, lungs, and kidney. Clearance was calculated based on biexponential decay of activity from these organs (Table 3). The gallbladder retention data showed a high degree of variability from patient to patient. Consequently, two-compartment fits were performed for each patient and the average residence time of 0.16 hr was used in dosimetry calculations.

2. Since 11.2% of ^{99m}Tc activity was excreted through feces, it is assumed that 88.8% of activity will eventually be cleared from the body in urine. Based on the amount of activity excreted in the urine within 24 hr (Table 1), the amount of urine activity retained in the body as a function of time (Table 1) was then derived. This data was fitted to a biexponential curve and the kinetics of urinary clearance were calculated (Table 3).

3. The 11.2% activity cleared through the feces was assumed to enter the small intestine from the gallbladder. Subsequent clearance was modeled according to the GI model given in ICRP 30 (*12*).

4. The dose to urinary bladder was calculated using the dynamic bladder model of Cloutier et al. (*13*).

5. Activity in the remainder of the body was treated according to the method of Cloutier et al. (*13*).

Radiation dose estimates for the different target organs (Table 4) were calculated for 2 hr and 4.8 hr voiding intervals.

DISCUSSION

The neutral lipophilic [^{99m}Tc]ECD complex was rapidly taken up by the human brain and the maximum peak activity reached within 1 min after administration. The brain uptake at 5 min was 6.5% of the injected dose. The clearance of ^{99m}Tc activity from brain followed a biexponential decay mode. Forty percent of the brain activity washed out with a half-life of 1.3 hr while the remaining 60% of brain activity (3.8% of injected dose) had a slower washout rate with a half-life of 42.3 hr. These results are very much in agreement with the initial studies in nonhuman primates (*8*). Walovitch et al. (*14*) reported that the retention of [^{99m}Tc]ECD activity in the brain was related to in vivo metabolism. Based on in vitro incubation studies of [^{99m}Tc]ECD with monkey brain cortex, they observed that [^{99m}Tc] ECD was metabolized rapidly in the brain by a specific enzymatic pathway to a polar complex that is trapped.

Following i.v. administration, the blood clearance of [^{99m}Tc] ECD was very rapid and 10% of the injected dose remained in circulation at 5 min and <1% at 4 hr. Walovitch et al. (*15*) reported that the parent compound in blood was rapidly converted to the polar metabolite and by 1 hr 90% of the ^{99m}Tc activity in the blood was associated with the metabolite. These results suggest that the brain input function was negligible

TABLE 2
Biodistribution of [^{99m}Tc]ECD in 16 Normal Human Subjects

Organ	Percent injected dose/organ					
	5 min	30 min	1 hr	2 hr	4 hr	24 hr
Blood	10.1 ± 6.4	7.4 ± 2.9	4.9 ± 1.0	—	1.0 ± 0.4	0.2 ± 0.2
Brain	6.5 ± 1.9	5.8 ± 1.7	5.2 ± 1.3	4.8 ± 1.2	3.8 ± 0.7	2.2 ± 0.3
Liver	17.0 ± 7.0	10.0 ± 5.0	6.2 ± 3.5	4.4 ± 2.2	2.5 ± 1.2	1.5 ± 0.7
Kidney	8.8 ± 2.8	4.0 ± 2.2	3.3 ± 1.7	1.8 ± 1.2	0.7 ± 0.4	0.4 ± 0.3
Lungs	4.7 ± 2.8	2.0 ± 1.8	1.4 ± 1.2	0.9 ± 0.7	0.6 ± 0.4	0.3 ± 0.2
Gall bladder	0.9 ± 1.1	2.6 ± 2.1	3.3 ± 2.6	4.2 ± 3.1	1.8 ± 1.4	0.2 ± 0.2
Heart	0.7 ± 0.6	0.5 ± 0.3	0.3 ± 0.2	0.2 ± 0.2	0.1 ± 0.1	—
Thyroid	0.3 ± 0.3	0.2 ± 0.2	0.1 ± 0.2	0.1 ± 0.1	0.1 ± 0.1	—
Legs	8.5 ± 4.1	6.8 ± 3.2	4.9 ± 2.3	3.0 ± 1.4	1.3 ± 0.6	0.3 ± 0.5
Bladder	8.0 ± 3.9	26 ± 12	21 ± 20	10 ± 16	3.1 ± 2.8	0.1 ± 0.1
Total body	100	94 ± 4	70 ± 17	43 ± 8	28 ± 5	18 ± 7

within a few minutes after the injection of the tracer and no further brain uptake of [^{99m}Tc]ECD was possible. At 1 hr postinjection, since the total blood activity of ^{99m}Tc was only 5% of the injected dose it is safe to assume the ^{99m}Tc brain activity was entirely because of the tracer trapped within the brain.

The excretion of the tracer from the body was very rapid. Fifty percent of the ^{99m}Tc activity appeared in the urine within 2 hr and 65% by 4 hr. This rapid urinary excretion of ^{99m}Tc activity was related to the metabolic transformation of the tracer since only the polar metabolites were identified in the urine (*15*). The hepatobiliary excretion of [^{99m}Tc]ECD was ~11% of the injected activity. The ^{99m}Tc activity in the lungs and muscle was negligible within 1–2 hr after the injection of the tracer. The total-body retention of ^{99m}Tc activity was <30% at 4 hr.

The radiation dose estimates for different organs summarized in Table 4 indicate that the urinary bladder wall and the gallbladder wall are the critical organs and the dose to the bladder wall depends on the time and frequency of voiding. For 20 mCi (0.74 GBq) of [^{99m}Tc]ECD administered and a voiding interval of 2 hr, the estimated radiation dose to the urinary bladder wall is 2.2 rad and gallbladder wall is 1.8 rad.These results indicate that the radiation dosimetry of [^{99m}Tc]ECD will be quite favorable for the administration of up to 20–40 mCi (0.74–1.48 GBq) for SPECT imaging studies.

The biodistribution studies reported here are part of Phase I study to evaluate the safety of [^{99m}Tc]ECD. The protocol did not include brain SPECT imaging studies. It is therefore difficult to infer from the biodistribution studies if ^{99m}Tc-ECD brain uptake reflects rCBF. However, dual labeled autoradiographic studies in monkey brain with ^{99m}Tc-ECD and ^{14}C-iodoantipyrine were performed by Walovitch et al. (*8*) to determine if ^{99m}Tc-ECD is a marker of rCBF. They observed that the distribution pattern for both tracers was similar and that the ratio of cortical grey to white matter was 4–5 to 1 for both tracers. The initial SPECT imaging studies in normal human subjects (*16*) suggests that [^{99m}Tc]ECD is useful to assess rCBF in humans. In addition,

TABLE 3
Biologic Clearance of ^{99m}Tc Activity from Different Organs Based on Two Compartment Analysis of [^{99m}Tc]ECD Biodistribution

Organ	Compartment 1		Compartment 2	
	% cleared	$T_{½b}$ (hr)	% cleared	$T_{½b}$ (hr)
Brain	2.7	1.3	3.8	42.3
Kidneys	8.7	0.46	0.8	22.7
Liver	16.3	0.43	3.3	19.9
Lungs	4.5	0.24	1.1	9.4
Urinary bladder	69.9	1.10	18.9	74.9
Total body	68.0	0.96	32.0	36.1

TABLE 4
Radiation Dose Estimates Following Intravenous Injection of [^{99m}Tc]ECD

Organ	Estimated radiation dose			
	2 hr*		4.8 hr*	
	mGy/mBq	rad/mCi	mGy/mBq	rad/mCi
Brain	0.0055	0.020	0.0055	0.020
Gall bladder wall	0.025	0.091	0.025	0.092
Lower large intestinal wall	0.013	0.047	0.015	0.055
Small intestine	0.0094	0.035	0.010	0.038
Upper large intestinal wall	0.016	0.061	0.017	0.063
Kidneys	0.0073	0.027	0.0074	0.027
Liver	0.0053	0.020	0.0054	0.020
Lungs	0.0020	0.0076	0.0020	0.0076
Ovaries	0.0054	0.022	0.0080	0.030
Red marrow	0.0024	0.0087	0.0027	0.0098
Bone surfaces	0.0034	0.013	0.0038	0.014
Testes	0.0022	0.0081	0.0036	0.013
Thyroid	0.0035	0.013	0.0035	0.013
Urinary bladder wall	0.030	0.11	0.073	0.27
Total body	0.0024	0.0089	0.0029	0.011

* Radiation dose estimates were calculated based on voiding interval of 2 or 4.8 hr.

studies comparing [^{99m}Tc]ECD to ^{99m}Tc hexamethylpropyleneamine oxime (HM-PAO) in normals (*17*) and xenon-133 in patients with stroke (*18*) suggest that [^{99m}Tc]ECD brain SPECT images are useful for clinical evaluation of rCBF.

REFERENCES

1. Ell PJ, Jarritt PH, Costa DC, Cullum ID, Lui D. Functional imaging of the brain. *Semin Nucl Med* 1987; 17:214–229.
2. Holman BL, Lee RGL, Hill TC, et al. A comparison of two cerebral blood flow tracers, N-isopropyl I-123 p-iodoamphetamine and I-123 HIPDM. *J Nucl Med* 1984; 25:25–30.
3. Volkert WA, Hoffman TJ, Seger RM, Troutner DE, Holmes RA. ^{99m}Tc-propylene amine oxime (^{99m}Tc-PnAO); a potential brain radiopharmaceutical. *Eur J Nucl Med* 1984; 9:511–516.
4. Sharp PF, Smith FW, Gemmell HG, et al. Technetium-99m HM-PAO sterioisomers as potential agents for imaging regional cerebral blood flow: human volunteer studies. *J Nucl Med* 1986 27:171–177.
5. Kung HF, Molnar M, Billings J, et al. Synthesis and biodistribution of neutral lipid-soluble Tc-99m complexes that cross the blood brain barrier. *J Nucl Med* 1984; 25:326–332.
6. Lever SZ, Burns LH, Kervitsky TM, et al. Design, preparation, and biodistribution of a technetium-99m triaminedithiol complex to assess regional cerebral blood flow. *J Nucl Med* 1985; 26:1287–1294.
7. Cheesman EH, Blanchette MA, Ganey MV, Maheu LJ, Miller SJ, Watson AD. Technetium-99m ECD: ester-derivatized diaminedithiol Tc Complexes for imaging brain perfusion [Abstract]. *J Nucl Med* 1988; 29:788.
8. Walovitch RC, Williams SJ, Morgan RA, Garrity ST, Cheesman EH. Pharmacological characterization of Tc-99m ECD in non-human primates as a new agent for brain perfusion imaging [Abstract]. *J Nucl Med* 1988; 29:788.
9. Vallabhajosula S, Stritzke P, Goldsmith SJ, Vaknine R, Lipszyc H. Tc-99m-ECD: a new brain agent: in vivo kinetics and biodistribution in normal human subjects [Abstracts]. *J Nucl Med* 1988; 29:921.
10. Nadler SB, Hidalgo JV, Bloch T. Prediction of blood volume in normal human adults. *Surgery* 1962; 51:224–232.
11. Snyder WS, Ford MP, Warner GG, Watson SB. "S" Absorbed dose per unit accumulated activity for selected radionuclides and organs. *MIRD Pamphlet No 11.* New York: The Society of Nuclear Medicine, Inc. 1975.
12. International Commission on Radiological Protection: limits for intakes of radionuclides by workers. ICRP 30, Part 1. New York: 1978. Pergamon Press.
13. Cloutier R, Smith S, Watson E, Snyder W, Smith E. Dose to the fetus from radionuclides in the bladder. *Heath Phys* 1973; 25:147–161.
14. Walovitch RC, Makuch J. Knapik G, Watson AD, Williams SJ. Brain retention of Tc-99m-ECD is related to in vivo metabolism [Abstract]. *J Nucl Med* 1988; 29:747.
15. Walovitch RC, Hall KM, O'Toole JJ, Williams SJ. Metabolism of ^{99m}Tc-ECD in normal volunteers [Abstract]. *J Nucl Med* 1988; 29:747.
16. Leveille J, Demonceau G, Rigo P, et al. Brain tomographic imaging with Tc-99m-ethyl cysteinate dimer (Tc-ECD): a new stable brain perfusion agent [Abstract]. *J Nucl Med* 1988; 29:758.
17. Ell PJ, Costa DC, Lui D. First results of a comparison between ^{99m}Tc-ECD and ^{99m}Tc-HMPAO [Abstract]. *J Nucl Med* 1988; 29:912.
18. Garrett K, Villanueva J, Kuperus J, Giombetti R, Mena I. A comparison of regional cerebral blood flow with Xe-133 to SPECT Tc-99m-ECD [Abstract]. *J Nucl Med* 1988; 29:913.