

Biodistribution, Dosimetry, and Safety of Myocardial Perfusion Imaging Agent $^{99m}\text{TcN-NOET}$ in Healthy Volunteers

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$^{99m}\text{TcN-NOET}$ (bis[N-ethoxy,N-ethyl]dithiocarbamate nitrido technetium (V)) has been proposed for myocardial perfusion imaging. Biodistribution, safety, and dosimetry were studied in 10 healthy volunteers (5 at rest and 5 during exercise). **Methods:** Biodistribution was studied by acquiring dynamic images up to 60 min after injection and whole-body images up to 24 h after injection. The MIRDSE3 analysis program was used for radiation dosimetry calculations. **Results:** Safety parameters measured to 48 h after injection revealed no clinically significant changes. Cardiac uptake of $^{99m}\text{TcN-NOET}$ was high (2.9%–3%), with biologic half-life of 210–257 min on average. Lung uptake of $^{99m}\text{TcN-NOET}$ was higher (10%–20%) but, on average, biologic half-life was shorter (1–77 min). Clearance from the blood was rapid (5% by 5 min). Radiation dosimetry calculations indicated an effective absorbed dose of 5.11×10^{-3} mSv/MBq at rest and 5.38×10^{-3} mSv/MBq after exercise. **Conclusion:** $^{99m}\text{TcN-NOET}$ exhibits high cardiac uptake and an estimated effective absorbed dose comparable with that of the other ^{99m}Tc -labeled compounds used in myocardial perfusion imaging.

Key Words: $^{99m}\text{TcN-NOET}$; myocardial perfusion agent; biodistribution; dosimetry

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The neutral, lipophilic technetium complex $^{99m}\text{TcN-NOET}$ (bis[N-ethoxy,N-ethyl]dithiocarbamate nitrido technetium (V)) has been proposed as an agent for studying myocardial perfusion in humans (1,2). Preclinical studies indicated good heart uptake of $^{99m}\text{TcN-NOET}$ in different animal species (1). In the dog, $^{99m}\text{TcN-NOET}$ heart activity correlated well with regional coronary blood flow measured by the microsphere technique (3–5). This was true for a wide range of flows. The first-pass extraction fraction in the dog was comparable with that of ^{201}Tl (0.75–0.85) (3). Reperfusion studies (3,4) and low-flow delayed studies (6) indicated a $^{99m}\text{TcN-NOET}$ redistribution phenomenon comparable with that of ^{201}Tl . This redistribution phenomenon has been demonstrated in humans, and the first clinical studies

confirmed the similarity in behavior between $^{99m}\text{TcN-NOET}$ and ^{201}Tl (2,7). However, the cellular binding mechanisms are different. $^{99m}\text{TcN-NOET}$ appears to bind to the cell membranes (8,9) but with a particular affinity for membrane calcium channels, although this binding is not energy dependent (10).

The aim of this study was to determine the biodistribution, dosimetry, and safety of $^{99m}\text{TcN-NOET}$ in clinical conditions in healthy volunteers, during exercise and at rest.

MATERIALS AND METHODS

Study Population

The study involved 10 healthy volunteers (6 nonlactating women using contraception, 4 men; age range, 24–60 y; mean, 36 ± 11 y; average weight, 66 ± 12 kg; weight range, 44–84 kg; average height, 160 ± 9 cm; height range, 157–182 cm; average body area, 1.7 ± 0.2 m²; area range, 1.4–2.0 m²). The medical histories of the volunteers were checked, and they were examined to ensure that there were no risk factors or symptoms of cardiovascular disease. A clinical examination and a 12-lead electrocardiogram were performed in all cases. Volunteers were accepted for the study after a second visit, once the results of the following biologic tests had been obtained: electrolytes, urea, creatinine, complete blood count, cholesterol, triglycerides, aspartate transaminase and alanine transaminase, creatine phosphokinase, lactate dehydrogenase (LDH), alkaline phosphatase, and γ -glutamyl transpeptidase (GGT). All subjects gave their informed consent and approval was obtained from the Université de Grenoble ethical committee.

After randomization, 5 subjects received an injection of $^{99m}\text{TcN-NOET}$ at rest (group I) and the other 5 subjects received an injection during exercise (group II). These 2 groups were comparable in terms of initial characteristics apart from their ages (group I, 40 ± 14 y; group II, 33 ± 7 y; $P < 0.05$) and heights (group I, 163 ± 6 cm; group II, 175 ± 8 cm; $P < 0.05$).

Preparation of $^{99m}\text{TcN-NOET}$

Labeling. The $^{99m}\text{TcN-NOET}$ was prepared extemporaneously from a kit obtained from CIS-Biointernational (Gif sur Yvette, France). This kit contained 3 vials. Vial A held stannous chloride dihydrate (technetium-reducing agent) (0.02 mg); 1,2-diaminopropane-N,N,N',N'-tetraacetic acid (5.00 mg); succinyl dihydrazide (10.00 mg); and sodium phosphate buffer, pH 7.8 (1.00 mL). Vial B held N-ethoxy,N-ethyl dithiocarbamate of sodium, monohydrate (12.00 mg) and water sufficient for injection (1.20 mL). Vial C held

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dimethyl B cyclodextrin (solubilizing agent) (12.00 mg) and water sufficient for injection (1.20 mL).

Vial A was labeled with a solution of 1–3 mL $^{99m}\text{TcO}_4^-$ with an activity of 3700–4440 MBq (100–120 mCi). The vial was left at room temperature for 15 min; then 1 mL solution B and 1 mL solution C were added. After 10 min at room temperature, physiologic saline (9% NaCl) was added to the resulting solution to give a final volume of 8 mL. Finally, the activity of the final solution was counted before injection so that a volume corresponding to an injected activity of 555–925 MBq (15–25 mCi), i.e., between 1 and 1.5 mL, could be measured.

Quality Control of $^{99m}\text{TcN-NOET}$. Before giving the injection to each healthy volunteer, 2 μL solution C were placed on a reverse-phase chromatography plate (Whatman KCF18; Whatman International, Maidstone-Kent, UK). An 8:2 (vol/vol) mixture of methanol and 0.5 mol ammonium acetate was used for development.

$^{99m}\text{TcN-NOET}$ has an R_f of 0.25 ± 0.05 . The unreacted pertechnetate migrated to the front, and the impurities migrated with R_f values of 0.47 ± 0.05 and 0.80 ± 0.05 . After 30-min migration, the radioactivity of the chromatography plate was counted using a Berthold counter (Berthold, Bad Wildbad, Germany). The activities of $^{99m}\text{TcN-NOET}$ (A- $^{99m}\text{TcN-NOET}$), the impurities (A-Imp), and the pertechnetate (A-Per) were measured. The radiochemical purity (RCP) indicating the labeling yield of $^{99m}\text{TcN-NOET}$ was obtained by:

$$\text{RCP} = \text{A-}^{99m}\text{TcN-NOET} / [\text{A-Imp} + \text{A-Per}] + \text{A-}^{99m}\text{TcN-NOET}.$$

The injection could be administered only if the RCP was more than 90%, which was always the case (average RCP = $96\% \pm 2\%$).

Administration Protocol. After a 12-h fast, a cannula was placed in the arm of each of the 10 subjects, and 555–925 MBq (15–25 mCi) $^{99m}\text{TcN-NOET}$ was administered by slow intravenous injection over a period of 1 min. This injection was given to 5 subjects at rest and to 5 subjects performing a bicycle ergometer exercise test, with work loads increasing incrementally by 50 W, so as to reach at least 85% of the maximum age-predicted heart rate. The average work load reached by the 5 subjects in group II was 200 ± 47 W, for a maximum heart rate of 169 ± 7 beats/min, in other words $91\% \pm 3\%$ of the maximum age-predicted heart rate. Arterial blood pressure was on average 174 ± 4 mm Hg systolic and 94 ± 5 mm Hg diastolic, giving a heart rate–blood pressure product of $29,450 \pm 1589$. The average duration of exercise was 9.7 ± 2.5 min.

Safety Parameters

Clinical Follow-up. All undesirable effects related to the administration of the agent were recorded. A full clinical examination was performed before the injection was administered and 48 h after injection. Blood pressure and heart rate were measured 5 min before injection, then at 5, 10, 20, and 30 min and 1, 4, 12, 24, and 48 h after injection of $^{99m}\text{TcN-NOET}$. An electrocardiogram was obtained before the injection and 30 min and 24 h after injection. Electrocardiographic monitoring (by oscilloscope) took place continuously for the first hour after administration of the product.

Biologic Follow-up. A cannula was inserted in the arm opposite the one in which the $^{99m}\text{TcN-NOET}$ was injected. Blood samples were taken 5 min before the injection, then 4 and 48 h after injection for the following analyses: electrolytes, urea, creatinine, complete blood count, cholesterol, triglycerides, aspartate transaminase and alanine transaminase, creatine phosphokinase, LDH, alkaline phosphatase, and GGT. Creatinine clearance was measured from urine samples taken for 24 h before injection and on the

second day after injection. Urine samples were also collected 24, 48, and 72 h after injection. These samples were frozen and later analyzed for enzymes originating in the epithelium of the renal tubules (N-acetylglucosaminidase, alanine aminopeptidase, GGT, and LDH) and α_1 -microglobulin to check for any nephrotoxicity.

Pharmacokinetics

Radioactivity in Blood and Blood Metabolites. To determine clearance of $^{99m}\text{TcN-NOET}$ and its radioactive metabolites from the blood and plasma, blood was collected through the cannula in the arm opposite the one in which the drug was injected. Samples were taken 30 sec, 2, 5, 10, 20, and 30 min, and 1, 2, 4, 12, and 24 h after injection. These samples were measured for whole-blood radioactivity and plasma activity after centrifugation. The results are expressed as a percentage of the injected activity after correction for ^{99m}Tc decay.

Radioactivity in Urine and Urine Metabolites. Similarly, to determine clearance of $^{99m}\text{TcN-NOET}$ and its radioactive metabolites from the urine, radioactivity measurements were performed during different time periods (0–2, 2–4, 4–8, 8–12, and 12–24 h after injection). The results are expressed as a percentage of the injected activity after correction for ^{99m}Tc decay.

Biodistribution

To determine the biodistribution of $^{99m}\text{TcN-NOET}$, dynamic images were obtained using a γ camera with rectangular field of view with a low-energy, high-resolution, parallel-hole collimator (DXT; Sopha Medical Vision, Buc, France). The detector was positioned to obtain an anterior view of the thorax and upper abdomen, and images were obtained at a rate of 1 per min. Imaging was started as soon as possible after injection and continued until 60 min after injection. Regions of interest were identified manually to obtain time-related activity curves for the first 60 min for the heart, lungs, liver, spleen, gallbladder, kidneys, and urinary bladder. Subsequently, static whole-body images were obtained using the same γ camera 1, 2, 4, 6, and 24 h after injection to determine later changes in $^{99m}\text{TcN-NOET}$ uptake in the different organs (heart, lungs, liver, spleen, gallbladder, kidneys, urinary bladder, brain, thyroid, and muscles). All of these results are expressed as a percentage of the injected activity after correction for ^{99m}Tc decay.

Dosimetry

Dose estimates to the different organs mentioned in the previous paragraph and the whole-body effective dose were calculated on the basis of pharmacokinetic and biodistribution data using the MIRDOSE3 computer software (Oak Ridge Institute for Science and Education, Oak Ridge, TN). The time-related activity curves for the different organs, expressed as a percentage of the injected activity and corrected for ^{99m}Tc decay, were used for the dose calculations.

In the organs in which activity decreased with time, the dynamic curves of the first 60 min were fitted to a monoexponential model (CA-Cricket Graph III software; Computer Associates, New York, NY) as follows:

$$A_t = A_0 \times e^{-\lambda t},$$

where A_t is activity at a time point t , A_0 is initial activity, and t is postinjection time. This equation is used to calculate the biologic half-life (T_{bio}) of $^{99m}\text{TcN-NOET}$ in the organ of interest according to the equation:

$$T_{\text{bio}} = 0.693/\lambda.$$

The effective half-life of $^{99m}\text{TcN-NOET}$ (T_{Eff}) in this organ is then given by:

$$1/T_{\text{Eff}} = 1/T_{\text{Bio}} + 1/T_{\text{Tc}},$$

where T_{Tc} is the physical half-life of ^{99m}Tc , i.e., 6.03 h.

In the organs in which an accumulation of $^{99m}\text{TcN-NOET}$ was observed, T_{Bio} was considered infinite compared with the half-life of the radioisotope. Hence:

$$1/T_{\text{Eff}} = 1/T_{\text{Tc}}.$$

This effective half-life of $^{99m}\text{TcN-NOET}$ was used to determine the residence time of $^{99m}\text{TcN-NOET}$ (τ) in each organ according to:

$$\tau = 1.443 \times T_{\text{Eff}} \times A_{(t)\text{max}}/A_0,$$

where $A_{(t)\text{max}}/A_0$ is the maximum percentage of the injected activity present in the organ during the 24 h after injection.

Finally, the "source" organs—that is, the organs with maximum activity—and their corresponding residence times (τ) were introduced into the computer program, which calculated the absorbed dose received by the different organs and the equivalent whole-body absorbed dose. Dosimetry results are expressed in rem/mCi injected and in mSv/MBq injected.

Data Analysis

Results are expressed as mean \pm SD. Wilcoxon's nonparametric paired test was used to compare the different values measured over time within the same group. Mann and Whitney's nonparametric unpaired test was used to compare values for groups I and II.

RESULTS

Safety Parameters

No undesirable effects were reported by the subjects during the 48 h after injection of $^{99m}\text{TcN-NOET}$. No significant changes were found in vital signs (heart rate, blood pressure), clinical examination, electrocardiograms, or oscilloscope related to the administration of $^{99m}\text{TcN-NOET}$.

In terms of biologic aspects, no changes were measured, in particular with respect to leukocytes, creatininemia, creatinine clearance, and enzymes. Only the triglycerides showed a significantly higher level at 4 h after injection in group II, but such release is a normal occurrence after exercise (0.90 ± 0.36 g/L before exercise versus 1.10 ± 0.18 g/L 4 h later; $P = 0.045$).

Pharmacokinetics

Clearance of $^{99m}\text{TcN-NOET}$ from the blood was rapid, with less than 5% of the injected activity present 5 min after injection. There was no significant difference between the resting group and the exercise group (group I, $4.03\% \pm 1.15\%$ injected activity; group II, $3.60\% \pm 1.03\%$ injected activity) (Fig. 1). Plasma clearance of the drug followed blood clearance perfectly.

Total urine collected over 24 h was 66% higher in the exercise group than in the rest group (group I, 1.70 ± 0.51 L; group II, 2.83 ± 0.59 L; $P < 0.05$). The urinary clearance kinetics of $^{99m}\text{TcN-NOET}$ and its radioactive metabolites were identical in both groups (ANOVA, $P =$ not significant). There was no significant difference in cumulative clearance over 24 h between the 2 groups (group I, $5.52\% \pm 3.09\%$ injected activity; group II, $3.89\% \pm 1.91\%$ injected activity) (Fig. 2).

Biodistribution

The biologic half-life of $^{99m}\text{TcN-NOET}$ in the heart was 209.8 ± 57.8 min in group I and 564.6 ± 615.0 min in group II (not significant) (Figs. 3A and 3B). In the case of 4 of the 5 patients in group II, biologic half-life was superimposable (257 min on average) and comparable with that of group I.

The biologic half-life of $^{99m}\text{TcN-NOET}$ in the lungs was shorter than that in the heart, with no difference between the 2 groups (group I, 50.6 ± 22.3 min; group II, 76.6 ± 9.2 min) (Figs. 3A and 3B).

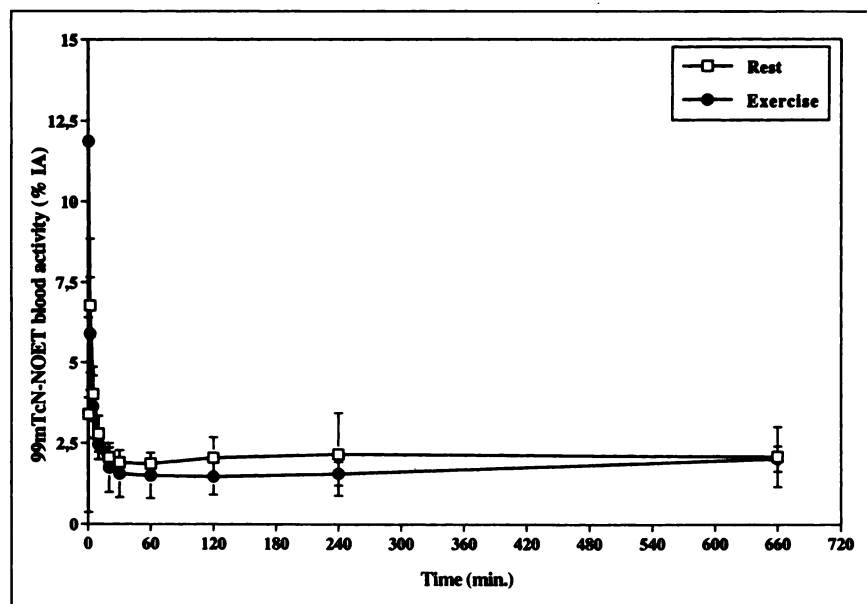


FIGURE 1. Blood clearance of $^{99m}\text{TcN-NOET}$. Blood clearance curve after injection at rest (\square) and exercise (\bullet) (mean \pm SD). IA = injected activity.

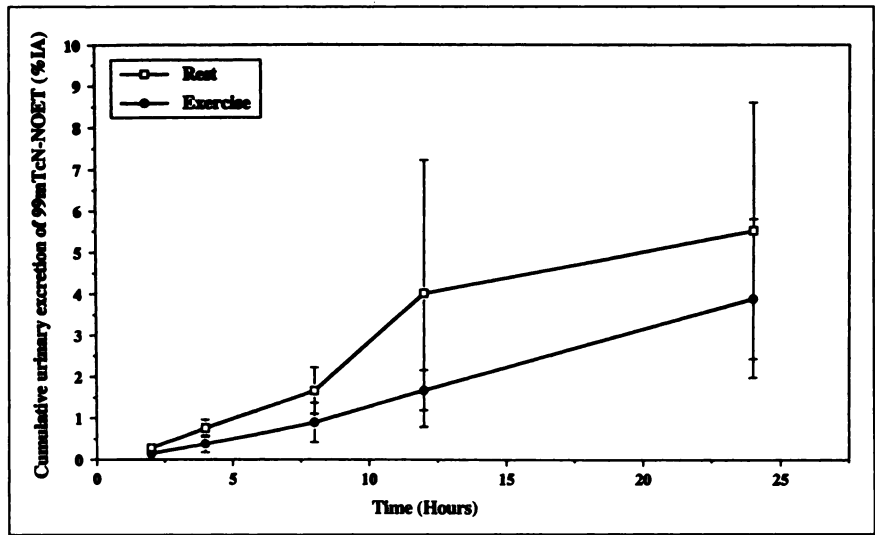


FIGURE 2. Cumulative urinary clearance of ^{99m}TcN-NOET in first 24 h after injection at rest (□) and exercise (●) (mean ± SD). IA = injected activity.

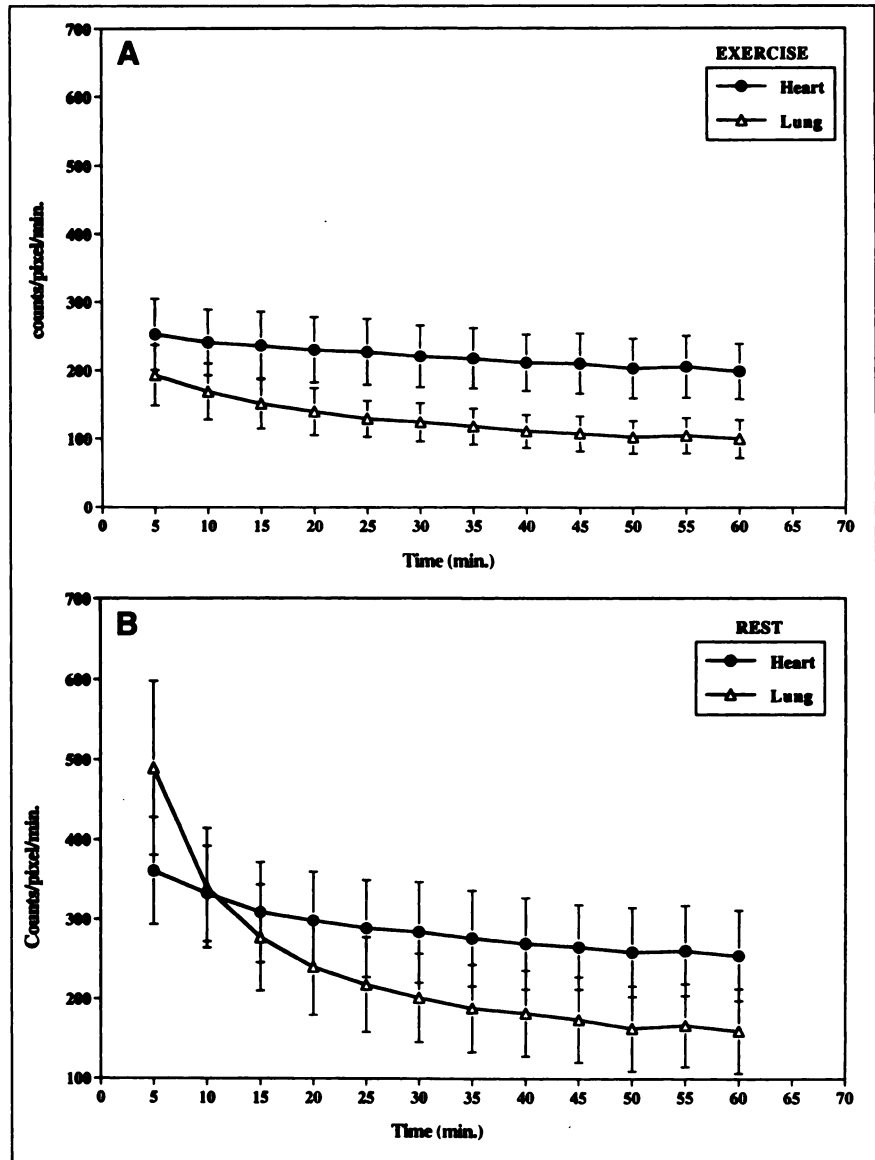


FIGURE 3. Activity curve in heart (●) and lungs (Δ) in first 60 min after injection of ^{99m}TcN-NOET after exercise (A) and at rest (B).

Uptake kinetics for the liver showed a gradual accumulation of $^{99m}\text{TcN-NOET}$, reaching a plateau at 30 min after injection at rest and between the 20–30 min after injection after exercise (not significant).

Heart uptake represented on average 3% of injected dose at 5 min after injection both at rest and after exercise (Table 1). This initial uptake was more than 2% of injected activity in every case (group I, 2.03%–3.75% injected activity; group II, 2.41%–3.57% injected activity) and fell gradually to less than 2% at 4 h after injection for group I ($1.7\% \pm 0.4\%$ injected activity) and at 6 h after injection for group II ($1.8\% \pm 0.5\%$ injected activity). The difference between the 2 groups was not significant.

Uptake by the lungs was substantial in the subjects at rest ($20.5\% \pm 1.7\%$ injected activity at 5 min). Lung uptake was lower after exercise ($10.6\% \pm 2.8\%$ injected activity; $P < 0.009$ versus subjects at rest). Uptake cleared rapidly in both groups, falling to 5% injected activity at 24 h after injection (group I, $4.9\% \pm 0.6\%$ injected activity; group II, $5.1\% \pm 1.1\%$ injected activity; not significant).

The delayed analyses confirmed the stabilization of liver activity after the first 30 min. It was not possible to visualize the gallbladder in any of the 10 subjects, on either the dynamic images obtained in the first 60 min or the whole-body images obtained between 1 and 24 h after injection (Fig. 4). On the other hand, upper abdominal activity represented on average 3.0%–5.7% of the injected activity in group I and 1.5%–3.8% in group II (not significant).

Although uptake by the kidneys represented on average 3% of injected activity at all time points, urinary activity (measured in the bladder) was low, about 0.5% of injected activity, and the same in both groups.

The heart-to-lung ratio at rest was more than 1 from 15 min after injection, reaching a maximum of 1.67 ± 0.37 at 1 h after injection (Table 2). After exercise, this ratio exceeded 1 from the fifth minute after injection (1.35 ± 0.37 ; $P = 0.008$ versus at rest) and reached 2.04 ± 0.39 at 60 min after injection (not significant compared with ratio at rest). The heart-to-liver ratio was highest at 5 min after injection and was the same for the exercise group and the rest group (1.45 ± 0.15 versus 1.36 ± 0.22 ; not significant). It dropped more rapidly at rest than after exercise (at 60 min: group I, 0.60 ± 0.07 ; group II, 0.94 ± 0.11 ; $P = 0.009$). The heart-to-spleen ratio remained constant and always exceeded 1, both at rest and after exercise (group I, 1.65 ± 0.73 to 1.68 ± 0.28 ; group II, 1.88 ± 0.26 to 1.73 ± 0.15 ; not significant).

Clearance of $^{99m}\text{TcN-NOET}$

Whole-body activity, corrected for ^{99m}Tc decay, remained constant between 0 and 24 h after injection, both at rest and after exercise, indicating that clearance of $^{99m}\text{TcN-NOET}$ was slow for the first 24 h. Nevertheless, at rest, urinary clearance of $^{99m}\text{TcN-NOET}$ was $5.52\% \pm 3.09\%$ injected activity for the first 24 h. After exercise, it was $3.89\% \pm 1.91\%$. By adding the percentage of the injected activity

TABLE 1
Biodistribution of $^{99m}\text{TcN-NOET}$ During First 24 Hours

Organ	Group	5 min	30 min	1 h	2 h	4 h	6 h	24 h
Heart	Rest	2.9 ± 0.7	2.6 ± 0.6	2.3 ± 0.6	2.1 ± 0.5	1.7 ± 0.4	1.4 ± 0.4	0.9 ± 0.3
	Exercise	3.0 ± 0.5	2.8 ± 0.6	2.6 ± 0.6	2.4 ± 0.5	2.1 ± 0.5	1.8 ± 0.5	1.2 ± 0.3
Lungs	Rest	20.5 ± 1.7	13.9 ± 1.1	8.9 ± 2.0	8.0 ± 1.8	7.2 ± 1.3	6.7 ± 1.2	4.9 ± 0.6
	Exercise	$10.6 \pm 2.8^*$	$8.4 \pm 2.2^*$	6.4 ± 1.6	6.1 ± 1.4	5.9 ± 1.5	5.5 ± 1.2	5.1 ± 1.1
Liver	Rest	9.1 ± 1.9	14.5 ± 2.1	15.3 ± 2.0	13.9 ± 1.2	13.4 ± 0.9	13.3 ± 0.9	14.1 ± 1.3
	Exercise	$5.3 \pm 0.4^*$	$6.9 \pm 0.4^*$	$7.3 \pm 0.5^*$	$7.7 \pm 0.8^*$	$8.0 \pm 1.6^*$	$8.3 \pm 1.6^*$	12.4 ± 3.2
Kidneys	Rest	—	—	3.3 ± 0.7	3.2 ± 0.8	2.9 ± 0.7	2.7 ± 0.8	2.9 ± 0.9
	Exercise	—	—	3.5 ± 1.5	3.4 ± 1.3	3.3 ± 1.5	3.2 ± 1.5	3.8 ± 1.6
Brain	Rest	—	—	3.5 ± 0.4	3.1 ± 0.5	2.5 ± 0.4	2.3 ± 0.4	1.7 ± 0.3
	Exercise	—	—	$2.0 \pm 0.2^*$	$2.0 \pm 0.2^*$	$1.7 \pm 0.2^\dagger$	$1.6 \pm 0.2^\dagger$	1.5 ± 0.2
Thyroid	Rest	—	—	0.9 ± 0.2	0.9 ± 0.2	0.9 ± 0.2	0.8 ± 0.2	0.6 ± 0.2
	Exercise	—	—	$0.5 \pm 0.2^\dagger$	$0.5 \pm 0.3^\dagger$	$0.5 \pm 0.4^\dagger$	$0.5 \pm 0.5^\dagger$	0.5 ± 0.6
Upper large intestine	Rest	—	—	3.0 ± 1.7	3.0 ± 1.5	5.7 ± 2.8	3.7 ± 1.5	5.7 ± 3.5
	Exercise	—	—	1.5 ± 1.3	1.6 ± 1.2	$1.9 \pm 2.3^\dagger$	2.0 ± 1.4	3.8 ± 2.3
Muscle (thigh)	Rest	—	—	10.8 ± 3.7	11.4 ± 3.6	12.3 ± 3.4	12.6 ± 3.8	11.3 ± 2.0
	Exercise	—	—	$26.0 \pm 4.0^*$	$25.5 \pm 3.7^*$	$24.2 \pm 3.8^*$	$23.5 \pm 3.8^*$	$16.6 \pm 3.1^*$
Spleen	Rest	—	—	0.6 ± 0.3	0.5 ± 0.2	0.4 ± 0.2	0.3 ± 0.1	0.3 ± 0.2
	Exercise	—	—	0.4 ± 0.3	0.3 ± 0.2	0.3 ± 0.2	0.3 ± 0.2	0.2 ± 0.1
Bladder	Rest	—	—	0.5 ± 0.1	0.7 ± 0.3	0.6 ± 0.1	0.7 ± 0.3	0.8 ± 0.3
	Exercise	—	—	0.4 ± 0.1	0.4 ± 0.2	0.4 ± 0.2	0.6 ± 0.2	0.7 ± 0.3

* $P < 0.01$, exercise vs. rest.

† $P < 0.05$, exercise vs. rest.

Results are expressed as percentage of injected activity \pm SD.

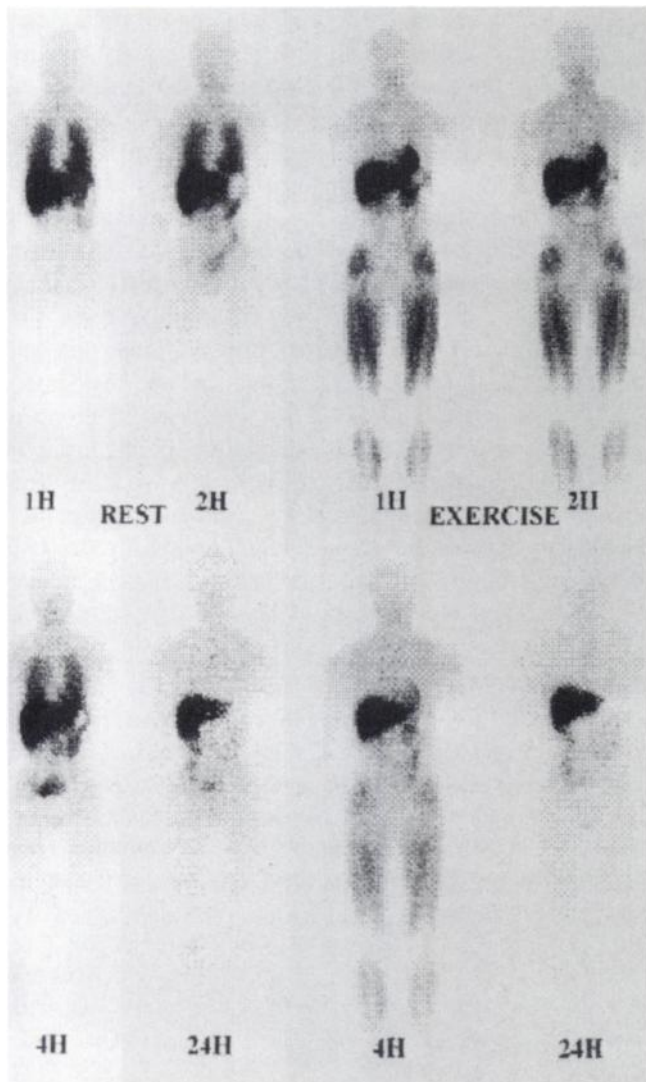


FIGURE 4. Anterior whole-body scans at 1, 2, 4, and 24 h after injection of $^{99m}\text{TcN-NOET}$ at rest and after exercise.

measured in the colon at 24 h ($5.7\% \pm 3.5\%$ injected activity at rest and $3.8\% \pm 2.3\%$ after exercise), total clearance of $^{99m}\text{TcN-NOET}$ in the first 24 h can be estimated at 7%–12% of injected activity.

TABLE 3
 $^{99m}\text{TcN-NOET}$ Residence Times in Organs

Organ	Rest		Exercise	
	Residence time (h)	Fraction of injected activity	Residence time (h)	Fraction of injected activity
Heart	0.09	0.028	0.13	0.030
Lungs	0.21	0.205	0.16	0.107
Liver	1.33	0.153	1.08	0.124
Brain	0.30	0.035	0.17	0.020
Large intestine	0.49	0.057	0.33	0.038
Muscles	1.09	0.126	2.26	0.260
Kidneys	0.29	0.033	0.33	0.038
Remainder	4.25	0.489	5.58	0.643

Dosimetry

The selected source organs, representing the main organs taking up $^{99m}\text{TcN-NOET}$, were the heart, lung, liver, kidney, brain, and upper abdomen (Tables 3 and 4).

The organs receiving the highest absorbed dose were the upper abdomen (at rest, 2×10^{-2} mSv/MBq; exercise, 1.5×10^{-2} mSv/MBq), kidney (at rest, 2×10^{-2} mSv/MBq; exercise, 2×10^{-2} mSv/MBq), and liver (at rest, 2×10^{-2} mSv/MBq; exercise, 1.5×10^{-2} mSv/MBq). Gonadal absorbed dose was estimated at rest and after exercise, respectively, at 0.2×10^{-2} mSv/MBq and 0.3×10^{-2} mSv/MBq for the testicles and 0.5×10^{-2} mSv/MBq and 0.5×10^{-2} mSv/MBq for the ovaries. For a complete heart scan with maximum injection of 1110 MBq (30 mCi), the absorbed dose to the gonads was 2.43–6.79 mSv. The effective whole-body absorbed dose for a complete heart scan with injection of 1110 MBq was between 5.67 mSv at rest and 5.97 mSv after exercise.

DISCUSSION

$^{99m}\text{TcN-NOET}$ is a new technetium complex for use in myocardial perfusion imaging. Its biologic behavior in the dog is comparable with that of ^{201}Tl . In particular, it exhibited a redistribution phenomenon characterized by relatively slow kinetics that are closer to those of ^{201}Tl than of teboroxime (3,4). The results of the first clinical trials

TABLE 2
 $^{99m}\text{TcN-NOET}$ Heart-to-Organ Ratios During First 60 Minutes

Ratio	Group	5 min	15 min	30 min	45 min	60 min
Heart-to-lung	Rest	0.75 ± 0.13	1.14 ± 0.18	1.45 ± 0.26	1.60 ± 0.35	1.67 ± 0.36
	Exercise	$1.35 \pm 0.37^*$	$1.61 \pm 0.42^\dagger$	1.81 ± 0.37	2.00 ± 0.41	2.04 ± 0.39
Heart-to-liver	Rest	1.36 ± 0.22	0.84 ± 0.06	0.67 ± 0.05	0.62 ± 0.04	0.60 ± 0.07
	Exercise	1.45 ± 0.15	$1.19 \pm 0.13^*$	$1.03 \pm 0.11^*$	$0.97 \pm 0.10^*$	$0.94 \pm 0.11^*$
Heart-to-spleen	Rest	1.65 ± 0.73	1.41 ± 0.50	1.46 ± 0.36	1.54 ± 0.26	1.68 ± 0.28
	Exercise	1.88 ± 0.26	1.70 ± 0.20	1.65 ± 0.18	1.72 ± 0.18	1.73 ± 0.15

* $P < 0.01$, stress vs. rest.

† $P < 0.05$, stress vs. rest.

TABLE 4
Dosimetry of ^{99m}TcN-NOET

Target organ	Rest total absorbed dose		Exercise total absorbed dose	
	mGy/MBq	rad/mCi	mGy/MBq	rad/mCi
Adrenals	5.74×10^{-3}	2.12×10^{-2}	6.17×10^{-3}	2.28×10^{-2}
Brain	5.34×10^{-3}	1.98×10^{-2}	3.52×10^{-3}	1.30×10^{-2}
Breasts	2.20×10^{-3}	8.15×10^{-3}	2.63×10^{-3}	9.72×10^{-3}
Gallbladder wall	8.47×10^{-3}	3.14×10^{-2}	8.10×10^{-3}	3.00×10^{-2}
Lower large intestine wall	3.35×10^{-3}	1.24×10^{-2}	4.12×10^{-3}	1.52×10^{-2}
Small intestine	5.80×10^{-3}	2.15×10^{-2}	5.88×10^{-3}	2.18×10^{-2}
Stomach	4.14×10^{-3}	1.53×10^{-2}	4.68×10^{-3}	1.73×10^{-2}
Upper large intestine wall	1.88×10^{-2}	6.96×10^{-2}	1.44×10^{-2}	5.32×10^{-2}
Heart wall	7.19×10^{-3}	2.66×10^{-2}	9.18×10^{-3}	3.40×10^{-2}
Kidneys	1.77×10^{-2}	6.54×10^{-2}	1.97×10^{-2}	7.30×10^{-2}
Liver	1.75×10^{-2}	6.46×10^{-2}	1.48×10^{-2}	5.49×10^{-2}
Lungs	5.45×10^{-3}	2.02×10^{-2}	5.09×10^{-3}	1.88×10^{-2}
Muscle	2.88×10^{-3}	1.06×10^{-2}	3.41×10^{-3}	1.26×10^{-2}
Ovaries	4.56×10^{-3}	1.69×10^{-2}	5.01×10^{-3}	1.85×10^{-2}
Pancreas	5.59×10^{-3}	2.07×10^{-2}	6.09×10^{-3}	2.25×10^{-2}
Red marrow	3.28×10^{-3}	1.22×10^{-2}	3.80×10^{-3}	1.41×10^{-2}
Bone surfaces	5.47×10^{-3}	2.02×10^{-2}	6.41×10^{-3}	2.37×10^{-2}
Skin	1.84×10^{-3}	6.82×10^{-3}	2.25×10^{-3}	8.31×10^{-3}
Spleen	3.84×10^{-3}	1.42×10^{-2}	4.56×10^{-3}	1.69×10^{-2}
Testes	2.19×10^{-3}	8.09×10^{-3}	2.84×10^{-3}	1.05×10^{-2}
Thymus	3.01×10^{-3}	1.11×10^{-2}	3.71×10^{-3}	1.37×10^{-2}
Thyroid	2.62×10^{-3}	9.71×10^{-3}	3.28×10^{-3}	1.21×10^{-2}
Urinary bladder wall	3.13×10^{-3}	1.16×10^{-2}	3.90×10^{-3}	1.44×10^{-2}
Uterus	3.92×10^{-3}	1.45×10^{-2}	4.61×10^{-3}	1.71×10^{-2}
Total body	3.63×10^{-3}	1.34×10^{-2}	4.03×10^{-3}	1.49×10^{-2}
	mSv/MBq	rem/mCi	mSv/MBq	rem/mCi
Effective absorbed dose equivalent	6.94×10^{-3}	2.57×10^{-2}	6.98×10^{-3}	2.58×10^{-2}
Effective absorbed dose	5.11×10^{-3}	1.89×10^{-2}	5.38×10^{-3}	1.99×10^{-2}

Radiation dose estimates are for reference adult for ^{99m}TcN-NOET (MIRDOSE-IBM-PC 3.0).

(2,8) indicated that this redistribution could possibly be used in vivo in humans. Given these numerous similarities to ²⁰¹Tl, ^{99m}TcN-NOET can be considered a potential technetium analog of ²⁰¹Tl.

The formulation was studied in 10 healthy volunteers. Radiochemical purity was greater than 90% ($96\% \pm 2\%$) in all cases. It was well tolerated with no adverse events. Measurements of clinical vital signs, hematology, blood

chemistry, and urinary parameters revealed no modifications apart from a temporary increase in α_1 -microglobulin in certain patients, but normal levels were re-established at 24 h after injection. These changes were not considered to be clinically significant.

Blood clearance was as rapid as in all myocardial perfusion imaging agents (11–16). Whole-body clearance of ^{99m}TcN-NOET was slow, because only 3%–5% of the injected activity was excreted in the urine by 24 h after injection. Taking into account activity in the colon at 24 h, total excretion in the first 24 h can be estimated at 7%–12% of injected activity, equally divided between the urinary and fecal routes. This clearance was much slower than in the case of the other technetium complexes [50%–65% for methoxyisobutyl isonitrile (12), approximately 40% for tetrofosmin (13)] and comparable with that of ²⁰¹Tl (11)

Biodistribution

Uptake by the heart was $3\% \pm 0.5\%$ of the injected activity at 5 min after injection, in other words twice that of the other technetium complexes except Q12 (14), but was still lower than that of ²⁰¹Tl. The biologic half-life in the myocardium of 210–260 min was of the same order as that of ²⁰¹Tl.

On the other hand, unlike the other technetium complexes, there was substantial uptake by the lungs, to the detriment of heart uptake in the first few minutes after injection. But given the more rapid washout for the lungs compared with the heart (51–77 min versus 210–257 min), the heart was clearly visible 30–45 min after injection. The heart-to-lung ratio at 45 min after injection was between 1.60 and 2, lower than this ratio in the case of other technetium complexes such as sestamibi (12) and tetrofosmin (13), but comparable with Q12 (14,15) and ²⁰¹Tl (12,15). The fact that images cannot be obtained until 30–45 min after injection, plus the existence of a redistribution phenomenon, may pose a problem in certain clinical cases in which rapid redistribution would decrease the ability of ^{99m}TcN-NOET to identify the presence or degree of ischemia. Although the first clinical study did not reveal a rapid redistribution phenomenon of ^{99m}TcN-NOET (2), particular attention should be given to this point in trials of phase 2 and phase 3.

^{99m}TcN-NOET activity in the kidneys was 3% of the injected activity at 24 h. The low activity visualized in the bladder as well as in the 24-h urine may indicate that the drug had been reabsorbed by the renal tubules, and the detection of α_1 -microglobulin in the urine supports this theory.

Dosimetry

Radiation dosimetry of ^{99m}TcN-NOET is comparable with that of the other technetium tracers sestamibi and tetrofosmin (13), Q12 (15), and Q3 (16) but considerably lower than that of ²⁰¹Tl (17). The organs receiving the highest absorbed dose were the upper large intestine, kidney, and liver, but these doses were much lower than those found for ²⁰¹Tl. The absorbed doses to the gonads were 6.79 mSv for the ovaries

after a maximum injection of 1110 MBq (30 mCi), much lower than those with a scan using ^{201}Tl .

CONCLUSION

Biodistribution of $^{99\text{m}}\text{TcN-NOET}$ and particularly its kinetics in the heart show that it behaves in a similar way to ^{201}Tl . But high lung uptake may present a problem in imaging, especially if there is a significant rapid redistribution of the radiopharmaceutical. The effective absorbed radiation dose for $^{99\text{m}}\text{TcN-NOET}$ is much lower than that of ^{201}Tl .

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REFERENCES

1. Pasqualini R, Duatti A, Bellande E, et al. Bis(dithiocarbamate) nitrido technetium-99m radiopharmaceuticals: a class of neutral myocardial imaging agents. *J Nucl Med.* 1994;35:334-341.
2. Fagret D, Marie PY, Brunotte F, et al. Myocardial perfusion imaging with technetium-99m-Tc NOET: comparison with thallium-201 and coronary angiography. *J Nucl Med.* 1995;36:936-943.
3. Ghezzi C, Fagret D, Arvieux CC, et al. Myocardial kinetics of TcN-NOET: a neutral lipophilic complex tracer of regional myocardial blood flow. *J Nucl Med.* 1995;36:1069-1077.
4. Vanzetto G, Calnon DA, Ruiz M, et al. Myocardial uptake and redistribution of $^{99\text{m}}\text{TcN-NOET}$ in dogs with either sustained coronary low flow or transient coronary occlusion: comparison with ^{201}Tl and myocardial blood flow. *Circulation.* 1997;96:2325-2331.
5. Glover DK, Ruiz M, Vanzetto G, Calnon DA, Watson DD, Beller GA. Comparison between Tl-201 and Tc-99m-NOET myocardial uptake during adenosine hyperemia in dogs with mild to moderate coronary stenoses [abstract]. *J Am Coll Cardiol.* 1997;29:442A.
6. Ghezzi C, Fagret D, Brichon PY, et al. Redistribution of bis(N-ethoxy, N-ethyl dithiocarbamate) nitrido technetium-99m (V), a new myocardial perfusion imaging agent: comparison with thallium redistribution [abstract]. *Circulation.* 1996;94:1302.
7. Vanzetto G, Marie PY, Leguludec D, et al. Tc99m-NOET: a new myocardial perfusion imaging agent that demonstrates redistribution: comparison with thallium 201 in patients with coronary artery disease [abstract]. *J Am Coll Cardiol.* 1998;31(suppl A):175A.
8. Uccelli L, Giganti M, Duatti A, et al. Subcellular distribution of technetium-99m-N-NOET in rat myocardium. *J Nucl Med.* 1995;36:2075-2079.
9. Johnson G, Allton IA, Nguyen KN, et al. Clearance of technetium $^{99\text{m}}\text{TcN-NOET}$ in normal ischemic-reperfused, and membrane-disrupted myocardium. *J Nucl Cardiol.* 1996;3:42-54.
10. Riou L, Ghezzi C, Mouton O, et al. Cellular uptake mechanisms of $^{99\text{m}}\text{TcN-NOET}$ in cardiomyocytes from newborn rats: calcium channel interaction. *Circulation.* 1998;98:2591-2597.
11. Atkins HL, Budinger TF, Lebowitz E, et al. Thallium-201 for medical use. Part 3: Human distribution and physical imaging properties. *J Nucl Med.* 1977;18:133-140.
12. Wackers FJT, Berman DS, Maddahi J, et al. Technetium-99m hexakis 2-methoxyisobutyl isonitrile: human biodistribution, dosimetry, safety, and preliminary comparison to thallium-201 for myocardial perfusion imaging. *J Nucl Med.* 1989;30:301-311.
13. Higley B, Smith FW, Smith T, et al. Technetium-99m-1,2bis(bis(2-ethoxyethyl) phosphino)ethane: human biodistribution, dosimetry and safety of a new myocardial perfusion imaging agent. *J Nucl Med.* 1993;34:30-38.
14. Rossetti C, Vanoli G, Paganelli G, et al. Human biodistribution, dosimetry and clinical use of technetium(III)-99m-Q12. *J Nucl Med.* 1994;35:1571-1580.
15. Gerson MC, Lukes J, Deutsch E, et al. Comparison of technetium 99m Q12 and thallium 201 for detection of angiographically documented coronary artery disease in humans. *J Nucl Cardiol.* 1994;1:499-508.
16. Rohe RC, Thomas SR, Stabin MG, et al. Biokinetics and dosimetry analysis in healthy volunteers for a two-injection (rest-stress) protocol of the myocardial perfusion imaging agent technetium 99m-labeled Q3. *J Nucl Cardiol.* 1995;2:395-404.
17. International Commission on Radiation Protection. Radiation dose to patients from radiopharmaceuticals. ICRP Publication 53. *Ann ICRP.* 1987;18:373.