Technetium-99m-1,2-bis[bis(2-Ethoxyethyl) Phosphino]Ethane: Human Biodistribution, Dosimetry and Safety of a New Myocardial Perfusion Imaging Agent

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A novel ^{99m}Tc complex (1,2-bis[bis(2-ethoxyethyl)phosphino] ethane, ^{99m}Tc-tetrofosmin) has been developed to replace ^{201}Tl in myocardial perfusion imaging. Biodistribution, safety and dosimetry of ^{99m}Tc-tetrofosmin were studied in 12 male volunteers, each at rest and during exercise. Safety parameters measured to 48 hr postinjection revealed no clinically significant long-term drug-related changes. Biodistribution was studied by acquiring whole-body or serial static images up to 48 hr postinjection. Technetium-99m-tetrofosmin shows good heart uptake (1.2%) with retention. Clearance is excellent from blood (<5% by 10 min), liver (<4.5% by 60 min) and lung. Sequestration of activity by skeletal muscle is enhanced during exercise. Radiation dosimetry calculations indicate that the effective dose, assuming a 3.5 hr bladder voiding period, is 32.9 × 10^{-3} rad/mCi (8.9 × 10^{-3} mSv/MBq) at rest and 26.7 × 10^{-3} rad/mCi (7.1 × 10^{-3} mSv/MBq) after exercise. Technetium-99m-tetrofosmin can produce high quality myocardial images from 5 min to several hours postinjection.

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Exercise myocardial scintigraphy is an established method for diagnosing and assessing the severity of coronary artery disease (CAD) (*1*). Thallium-201 is currently the most widely used radiopharmaceutical for myocardial perfusion scintigraphy. However, ^{201}Tl is not an ideal agent because of a low gamma photopeak energy (69–83 keV) that limits resolution and a relatively long half-life (73 hr) that limits the administered activity.

Technetium-99m-labeled radiopharmaceuticals promise certain advantages over ^{201}Tl. These include extemporaneous reconstitution from a kit when required, more

suitable photons (140 keV) for gamma camera imaging and, due to its shorter half-life (6.03 hr), reduced patient radiation dose for a higher injected activity. It has been claimed that a technetium-based agent could significantly improve the image quality compared with that obtainable with ^{201}Tl due to a twofold increase in resolution and an increased count rate resulting from a fourfold increase in administered activity (*2*).

Technetium-99m-1,2-bis[bis(2-ethoxyethyl)phosphino] ethane (tetrofosmin or P53) is a novel lipophilic technetium phosphine dioxo cation (^{99m}Tc(tetrofosmin)$_2$O$_2$]$^+$). The ligand (tetrofosmin, Fig. 1) has been formulated into a freeze-dried kit which yields an injection containing ^{99m}Tc-tetrofosmin on reconstitution with pertechnetate (*3*). Preclinical studies in the rat, guinea pig and minipig have shown that ^{99m}Tc-tetrofosmin has good heart uptake and retention, together with rapid clearance from liver, lung and blood. The formulation has been shown to have a very high safety margin in both single and repeated dose intravenous toxicology studies. The ligand has been demonstrated not to exhibit mutagenic potential in a range of in vitro and in vivo mutagenicity studies.

Previously, a limited human volunteer study was performed using a different formulation which yielded ^{99m}Tc-tetrofosmin. This study in three healthy male volunteers indicated the potential of this novel technetium complex (*4*).

Unlike ^{201}Tl, the myocardial distribution of ^{99m}Tc-tetrofosmin does not alter rapidly with time and hence diagnosis of reversible myocardial ischemia could not be achieved with a single injection of the reconstituted kit. Consequently, in clinical practice it will be necessary to administer two doses of the agent during a complete diagnostic protocol.

The present study was designed to establish the biodistribution, dosimetry and safety of this new ^{99m}Tc complex, produced using a freeze-dried formulation, in volunteers submitted to physical conditions similar to those required for a diagnostic study.
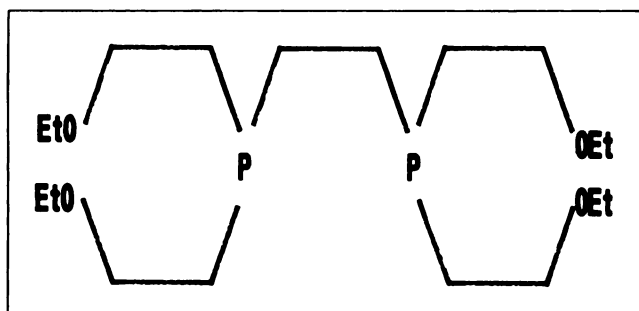
FIGURE 1. The structure of the ligand 1,2-bis[bis(2-ethoxy-ethyl)phosphino]ethane = tetrofosmin = (P53).

METHODS

Study Population

A total of 12 healthy male volunteers, mean age 28 ± 4 (range 22–35) yr, recruited from the local populations were studied at two centers (Northwick Park Hospital, Harrow, UK and Aberdeen Royal Infirmary, Scotland). The average weight of the volunteers was 71 ± 10 kg (range 58–90 kg). Each volunteer gave written informed consent. Approval of the trial was received from local ethical committees and the Administration of Radioactive Substances Advisory Committee (ARSAC) of the Department of Health (UK) prior to study commencement.

Volunteers were requested to report immediately to a supervising physician any unusual symptoms that they experienced following the administration of the agent. Volunteers remained under constant medical supervision for the first 12 hr postinjection, but were allowed to go home after that time.

Test Article

The agent was prepared from a freeze-dried kit* (*Myoview*™, Amersham International plc) by reconstitution with approximately 6 ml of a sterile sodium pertechnetate solution containing 5.1–9.9 mCi (190–370 MBq) of ^{99m}Tc. This was prepared by diluting the eluate from a ^{99m}Tc generator (Amertec II, Amersham International plc) with 0.9% saline. The vial was shaken gently to ensure complete dissolution of the lyophilized powder and allowed to stand at room temperature (15–25°C) for 15 min.

Radiochemical purity (RCP) was determined before and after use. The RCP method consisted of a Gelman ITLC/SG strip (2.0–2.5 cm × 20 cm) eluted using ascending chromatography with a fresh solution of 35:65 acetone/dichloromethane. Through use of this system, free pertechnetate runs with the solvent front, ^{99m}Tc-tetrofosmin complex runs to the middle portion and reduced hydrolyzed ^{99m}Tc and other hydrophilic complexes remain at the origin.

The reconstituted injectate was routinely used within 2 hr of reconstitution when the mean RCP was 96% ± 2%. However, adequate RCP (exceeding 90%) is maintained for 8 hr post-reconstitution.

Administration Protocol

Every volunteer received an injection of 3.7–4.7 mCi (140–170 MBq) (mean 4.1 ± 0.2 mCi) in a volume of 2.4 to 5 ml on each of two occasions. The total chemical dose administered to

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* Each kit contained 0.23 mg tetrofosmin, 30 μg stannous chloride dihydrate, 0.32 mg disodium sulphosalicylate, and 1.0 mg sodium gluconate, pH adjusted before lyophilization and sealed under an atmosphere of nitrogen.

each volunteer ranged from 40% to 82% (mean 61% ± 11%) of a single vial at rest and from 40% to 87% (mean 59% ± 16%) of a single vial during exercise. The total cumulative chemical dose (sum of rest and exercise injection) ranged from 88% to 162% (mean 120% ± 29%) of the total contents of a single vial.

Following an overnight fast, injections were performed both at rest, each subject being injected intravenously with the agent while lying supine, and within the next 7–14 days during a period of sub-maximal graded exercise (limited by achieving 85% age-predicted maximum heart rate, fatigue or dyspnea). Exercise was undertaken either supine using a bicycle (Northwick Park) or erect using a treadmill (Aberdeen). After injection during exercise, the subject was encouraged to continue exercising for a further minute.

Subjects were allowed a light meal after approximately 4 hr in the study.

Safety Parameters

Vital signs, including pulse, temperature and blood pressure, were measured within 30 min prior to injection, and remeasured at 5, 10, 15, 30 min, 1, 2, 4, 6, 24 and 48 hr postinjection. A 12-lead electrocardiogram (ECG) was recorded 30 min prior to injection and at 24 and 48 hr postinjection. ECG was monitored discontinuously for the first 6 hr postinjection, using limb leads, in order to facilitate monitoring during imaging.

Baseline blood samples for hematology (including total and differential white blood cell, red blood cell and platelet count, hemoglobin and hematocrit) and biochemistry (including electrolytes, creatinine, urea, total protein, albumin, gamma-glutamyl-transferase, alkaline phosphatase, aspartate transaminase, alanine transaminase, creatine phosphokinase and lactate dehydrogenase) were taken within 5 min prior to drug administration and repeated at 30 min, 6, 12, 24 and 48 hr postinjection. The blood samples were taken via a cannula placed in the opposite arm to that in which the drug was administered. Urine samples (mid-stream) were also obtained and analyzed by dipstick methods for protein, glucose, blood cells, bilirubin and ketones.

Clearance Studies

Anti-coagulated blood was collected, from the opposite arm to that in which the injection was made, at the following times: −5 (baseline), 2, 5, 10, 20, 30 min and 1, 2, 4, 12 and 24 hr. Duplicate whole blood samples (0.5 ml) were processed for counting. After removal of the whole blood aliquot, the remainder of the sample was centrifuged and duplicate 0.5 ml plasma samples processed in a similar way. Data were corrected for background and decay. Whole blood and plasma activity were calculated in terms of percentage of administered activity in the estimated total blood (or plasma) volume.

Urine was collected, in plastic bottles containing preservative, for 48 hr after injection. This was divided into collections from baseline (pre-injection) and where possible, 0–2, 2–4, 4–8, 8–12, 12–24, and 24–48 hr. Radioactivity in these samples was determined by counting in a fixed, reproducible geometry system midway between opposing NaI detectors and was calculated in terms of percentage of administered activity per sample. Feces were collected for 48 hr postinjection and radioactivity in these samples was determined in a similar way to that used for determination of urinary activity.

Biodistribution Studies

Different techniques for imaging the biodistribution of ^{99m}Tc-tetrofosmin were used at the two centers.

Whole-body images were obtained at Northwick Park using an IGE 400AT gamma camera (400 mm FOV) fitted with a low-energy, diverging parallel-hole collimator to increase the lateral viewing aspect. Both anterior and posterior views were obtained. The overall time from starting the anterior view to finishing the posterior view was about 18 min.

At Aberdeen, an IGE 500A Maxicamera (500 mm FOV) was used with a parallel-hole, low-energy, general-purpose collimator. The imaging technique consisted of nine static images, six anterior covering the whole length of the body and three posterior with imaging of the legs omitted. There was considerable overlap between adjacent views. The complete sequence took 20–26 min. Imaging was started at 5, 30 min, 1, 2, 4, 8, 24 and 48 hr postinjection.

Qualitative Analysis of Images

All images were reviewed to determine the subjective biodistribution and determine which organs and tissues were clearly visible and warranted quantitative assessment. Additionally, all anterior whole-body images and static chest views were reviewed as unprocessed hardcopies by two blinded readers. Readers were asked to assess the general image quality and whether diagnostically useful myocardial images had been obtained.

Quantitative Analysis of Images

Total body and individual organ retention of ^{99m}Tc at the various imaging times were estimated using the geometric mean of anterior and posterior images, corrected for physical decay of ^{99m}Tc during the period from the time of injection to the mid-time of that scan.

Whole-Body Images. At Northwick Park, total counts and number of pixels within a region of interest (ROI) drawn around the entire body image were recorded. Total counts were corrected using an average background count per pixel obtained from four separate regions outside the body contour. At Aberdeen, total counts in the body image were estimated by summation of consecutive regions after allowance was made for overlapping areas of adjacent static views, and corrected for background as above.

Retention in Organs and Tissues. A number of specific organs exhibited significant uptake of ^{99m}Tc-tetrofosmin, at least in the early stages of the study. These were identified as heart, lungs, liver, gallbladder, kidneys, salivary glands, thyroid, urinary bladder and gastrointestinal tract. Skeletal muscle also showed significant uptake, but it was felt inappropriate to attempt to quantify this since it was difficult to determine a representative sample, particularly during the exercise study. For each scanning session, ROIs were drawn around each organ and the ROI counts and pixel number were recorded. A correction for body background activity was made using the counts-to-pixel ratio obtained from an appropriate ROI positioned close to the organ. For organs lying within the abdominal region, corrections were often applied because of overlap. For example, because of difficulty in distinguishing the right kidney due to the proximity of liver and gallbladder, the uptake in both kidneys was determined as twice that in the left kidney. The latter was more readily measured in the initial stages but, later on, the presence of activity in the gastrointestinal tract made kidney activity difficult to measure. Where overlap of organ activity occurred, the activity in the organ of lower concentration was determined from the full organ size and the estimated counts/pixel from a nonoverlapped site. This

method was used, for example, to determine the rapidly diminishing activity in the liver in the presence of gallbladder activity. In these conditions, gallbladder activity was determined by subtracting an adjacent liver background from counts in the gallbladder ROI.

Organ Ratios. Heart-to-lung and heart-to-liver ratios were calculated on a counts/pixel basis using the average count density for the whole organ. However, background clearance was rapid such that, in all individuals, at later time points, heart-to-background ratios became meaninglessly large. At each time point, data are presented only for individuals in whom adequate background activity could be determined. Hence, the mean data presented tend to significantly underestimate the true mean at later time points.

Dosimetry

Calculation of Biokinetic Data. Because of the time span involved in performing a single anterior and posterior scanning session, the mid-time of such a session was used for plotting whole-body and organ retention times. The geometric mean of the first whole-body anterior and posterior scans was taken to represent 100% of administered activity and all the organ geometric means and whole-body geometric means obtained from subsequent sessions were related to this value. Total body retention was corrected for the estimated activity in the gastrointestinal tract and urinary bladder to give retention for "total-body less contents of gastrointestinal tract and bladder." In some cases, this value was ascertained using estimated total excreted activity. These values and retention values in all the selected organs (including whole blood) were fitted empirically to multiexponential equations to facilitate the calculation of residence times (5) for dosimetry purposes.

From the estimates of total urine activity and total fecal plus gastrointestinal activity at 48 hr, values for f_u and f_F, the relative fractions of excreted activity passing via the urinary and fecal route respectively, where $f_u + f_F = 1$, were obtained separately for the rest and exercise studies. These values were required to implement the bladder (6,7) and gastrointestinal (8) dosimetry models. The gastrointestinal tract model allowing for input to the small intestine was used to estimate residence times in sections of the gut (9).

Dose Calculation. Dose estimates were based on the standard MIRD formalism (5). $S_{t \leftarrow s}$ values were available for all the source organs (10) identified in this study, except salivary glands. The S value for salivary glands as both source and target organ was calculated specially. Dose to salivary glands from activity in other organs, and vice versa, was ignored.

Computer software (MIRDOSE 2 (revised), Oak Ridge Associated Universities) was used with residence times obtained in the present study to give doses to 25 target organs per unit administered activity (mGy/MBq; rad/mCi). MIRDOSE 2, if required, calculates the bladder residence time directly from the exponential whole-body retention parameters and the value of f_u, and this method was used to vary the bladder voiding period to observe its effect on dose calculations.

Calculation of Effective Dose. Based on the results of dose estimates to various target organs (Table 3), a value for the effective dose was calculated for both the rest and exercise studies (11). In the calculations of effective dose, the procedure adopted by ICRP 53 (6), of using the mean value of male and female gonad doses, was used.

Data Evaluation

Data were analyzed to give group mean values and standard deviations. Statistical significance of differences was determined using Student's t- or paired t-test where appropriate, with $p < 0.05$ being considered significant.

A comparison of data obtained at the two centers and under the two physiological conditions generally indicated only minor differences between the two centers and hence data are presented separately for rest and exercise studies but are pooled for the two centers.

All safety data, in the form of vital signs, hematology and blood biochemistry, were compared on an individual volunteer basis separately. A comparison was made of pre- and postinjection values for each parameter monitored and changes between normal and abnormal ranges were determined. Data were analyzed to determine whether clinically significant drug-related trends could be detected.

RESULTS

Safety Data

No serious adverse reactions were reported. Only one volunteer reported *any* symptoms. This individual reported feeling slightly warm immediately after the initial (resting) injection (80% of complete vial) and was mildly nauseous between 12 and 24 hr postinjection. However, his temperature did not deviate from normal at any time postinjection. He also reported a "metallic" taste immediately after the second (exercise) injection (62% of complete vial). On neither occasion was this the highest dose administered to a volunteer. This "metallic" taste is an effect that has previously been reported following the administration of ^{99m}Tc cations (*12,13*) but with a more frequent incidence than seen in this study.

Vital Signs. No ECG abnormalities were reported following either first or second injection of the agent. There was no consistent drug-related effect on blood pressure or temperature.

In the rest study, a number of the volunteers (7/12) displayed a slight drop in pulse rate immediately (5 min) following injection, ranging from 3 to 12 bpm, but this was followed by a slight increase in pulse rate at 10 min postinjection (ranging from 1 to 12 bpm). It is probable that the reported initial decreases in pulse rate may reflect an elevated heart rate due to anxiety prior to injection which resolved soon after injection. There did not appear to be a consistent drug-related effect on pulse rate.

Hematology/Biochemistry. White blood cell (WBC) count elevation (within the normal range) was a common feature noted between 6 and 24 hr postinjection. The average percentage increase was reasonably consistent at about 50% after both rest and exercise.

Pre-injection WBC counts were similar for individual volunteers when entering both the resting and exercise arms of the protocol. It was concluded therefore that there might be a small drug-related effect on WBC counts, but that it was transient and of little clinical significance.

There were no clinically significant drug-related changes in any of the other hematology, blood biochemistry or urinalysis parameters determined.

Clearance Studies

Blood Clearance. Blood clearance (Fig. 2) was rapid such that by 10 min postinjection there was less than 5% of the injected dose in the whole blood volume for all volunteers. In the majority of volunteers, blood clearance was initially faster following exercise. Plasma clearance closely followed whole blood clearance. By 10 min postinjection, there was less than 3.5% of the injected dose in the total plasma volume.

Urinary Clearance. The initial rate of urinary clearance (Fig. 3) was approximately 50% higher in the resting study than in the exercise study, accounting for 13.1% ± 2.1% and 8.9% ± 1.7% of the injected dose by 2 hr postinjection, respectively ($p < 0.001$). However, by 48 hr postinjection an equivalent amount of the injected dose had been excreted in the urine under both physiological conditions (39.0% ± 3.7% rest, 40% ± 3.7% exercise).

Fecal Clearance. Cumulative fecal clearance was lower after exercise (range 16.7%–33.6%, mean 25.2% ± 5.6%) than the corresponding rest (range 26.3%–41.1%, mean 34.2% ± 4.3%) study ($p < 0.05$).

Whole-Body Clearance. Clearance from the whole body at 48 hr was 72% ± 5.5% (range 64%–79%) at rest and 67% ± 6.3% (range 56%–73%) after exercise. The relative importance of urinary and fecal excretion was roughly similar, each accounting for about 50% of total excreted activity.

Biodistribution

Qualitative Analysis of Images. Analysis of images (Fig. 4) indicated that good quality pictures of the heart can be
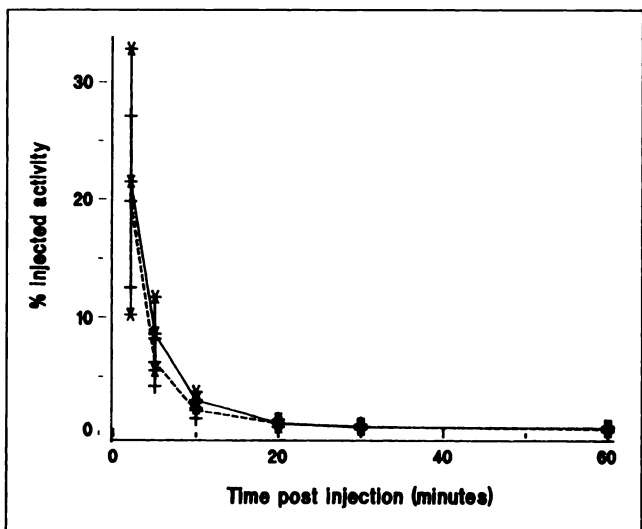

FIGURE 2. Blood clearance of ^{99m}Tc-tetrofosmin. Blood clearance curve of ^{99m}Tc-tetrofosmin after injection at rest (x—x) and exercise (+ - - - +) in 12 normal volunteers (mean ± s.d.). Data presented as % injected activity in estimated total blood volume. Activity in the blood was significantly lower following exercise only at 5 and 10 min postinjection ($p < 0.01$ – paired t-test).
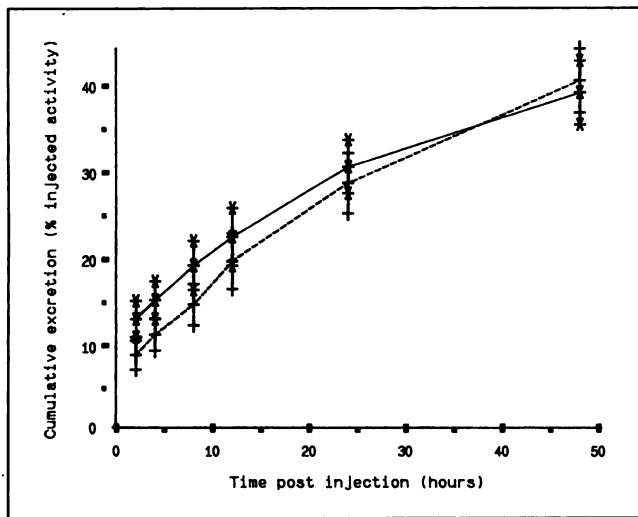
FIGURE 3. Urinary clearance of ^{99m}Tc-tetrofosmin. Cumulative urinary clearance of ^{99m}Tc-tetrofosmin after injection at rest (x—x) and exercise (+ - - - +) in 12 normal volunteers (mean ± s.d.). Cumulative urinary clearance was significantly lower after exercise at all times measured up to 24 hr ($p < 0.001$ up 12 hr, $p < 0.05$ at 24 hr), but crossed over such that total urinary excretion was higher at 48 hr after exercise ($p < 0.05$). All analyses were by paired t-test.

obtained from as early as 5 min postinjection and for several hours thereafter, even in volunteers showing uptake at the lower end of the range.

Relevant background clearance (blood, lung and liver) was rapid, which enhanced the myocardial image quality.

In most cases (10/12 both at rest and after exercise), images were considered to be of adequate quality to be of diagnostic value as early as 5 min postinjection. By 30 min, images from all volunteers were considered to be of high quality. After exercise, the biodistribution of ^{99m}Tc-tetrofosmin was obviously different from that observed in the resting study; there was less activity in certain organs, most noticeably liver, urinary bladder and salivary glands. The reduced activity in the liver, in particular, resulted in a clearer image of the heart (especially the apex) at an earlier stage than in the rest study. Lower uptake in some organs, but with higher whole-body retention, after exercise can be explained by an enhanced, rapid uptake and longer-term retention in muscle probably as a result of the increased blood flow especially to skeletal muscle induced by physical exercise. This deposition in muscle was clearly visible on the scans, being most marked in those muscle groups that had been utilized in the exercise regimen.

Quantitative Analysis of Images. Quantitative biodistribution data from the two centers were very similar. The only notable difference, 5-min liver uptake following exercise (4.2% ± 2.3% and 2.3% ± 0.5% for Northwick Park and Aberdeen, respectively), was observed under conditions of rapid dynamic change of organ ^{99m}Tc-tetrofosmin concentration when it was considered likely that small differences in data acquisition times could account for the inter-site differences.

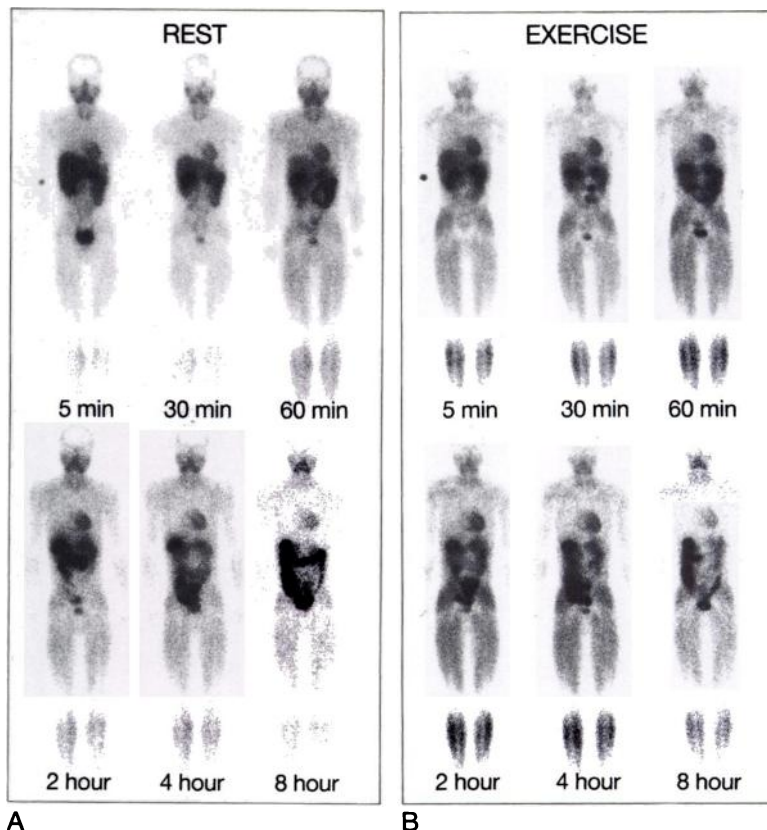Biodistribution data are presented in Table 1. In addition, where data were available, heart-to-lung and heart-

FIGURE 4. (A) Anterior whole-body scans at 5 and 30 min and 1, 2, 4 and 8 hr after injection of ^{99m}Tc-tetrofosmin at rest in a normal volunteer. (B) Anterior whole-body scans after injection of ^{99m}Tc-tetrofosmin at peak exercise in the same normal volunteer.

TABLE 1
Technetium-99m-Tetrofosmin Human Biodistribution (%Injected Activity, means ± s.d.)*

Organ	5 min	30 min	60 min	120 min	240 min	480 min	24 hr
Heart							
Rest	1.2 ± 0.3	1.2 ± 0.4	1.2 ± 0.4	1.0 ± 0.3	0.7 ± 0.3	0.5 ± 0.2	0.2 ± 0.1†
Exercise	1.3 ± 0.3	1.2 ± 0.2	1.1 ± 0.2	1.0 ± 0.2	0.8 ± 0.2	0.5 ± 0.2	0.3 ± 0.2§
Lung							
Rest	1.7 ± 0.7‡	1.0 ± 0.5§	0.7 ± 0.5**	0.3 ± 0.5	0.1 ± 0.2	ND	ND
Exercise	1.2 ± 0.4	0.7 ± 0.3¶	0.5 ± 0.3**	0.2 ± 0.2**	ND		
Liver							
Rest	7.5 ± 1.7††	4.5 ± 2.1‡‡	2.1 ± 1.0‡‡	0.9 ± 0.6§§	0.3 ± 0.1**¶	0.1 ± 0.2	ND
Exercise	3.2 ± 1.9	2.1 ± 1.0	1.0 ± 0.5†	0.5 ± 0.4§§	0.1 ± 0.1§§	ND	
Gallbladder							
Rest	0.8 ± 1.3	2.9 ± 2.0	5.2 ± 2.4‡	5.3 ± 2.7	4.1 ± 2.3§	4.4 ± 4.1¶	1.5 ± 2.0**
Exercise	0.5 ± 0.6	2.0 ± 1.0	3.0 ± 1.0	3.2 ± 1.0§	2.6 ± 1.6§	3.0 ± 1.9§§	1.1 ± 1.1***
Kidney							
Rest	6.2 ± 2.2	5.1 ± 1.7	4.1 ± 1.7‡	2.9 ± 1.1	1.9 ± 0.7§	1.3 ± 0.5¶	0.8 ± 0.5**
Exercise	4.9 ± 2.2	3.9 ± 2.4	2.8 ± 0.9	2.3 ± 1.0	1.7 ± 0.6§	1.5 ± 0.6§§	0.6 ± 0.4
Salivaries							
Rest	1.5 ± 0.7‡	1.2 ± 0.4‡	1.2 ± 0.5	1.2 ± 0.5‡	1.2 ± 0.5‡	1.0 ± 0.3	0.5 ± 0.2**
Exercise	0.9 ± 0.1	0.8 ± 0.2	0.9 ± 0.3	0.8 ± 0.2	0.8 ± 0.4	0.5 ± 0.2	0.5 ± 0.3¶
Thyroid							
Rest	0.3 ± 0.2‡	0.3 ± 0.2††	0.2 ± 0.1‡	0.2 ± 0.1¶	0.1 ± 0.2	ND	ND
Exercise	0.2 ± 0.1	0.2 ± 0.1†	0.1 ± 0.1¶	0.1 ± 0.1§§	ND	ND	ND
Gastrointestinal tract							
Rest	2.9 ± 2.3	6.9 ± 3.0¶	10.7 ± 2.7††	13.8 ± 5.0††	19.1 ± 6.2‡	22.6 ± 5.7††	23.6 ± 11.9
Exercise	2.0 ± 1.9	4.4 ± 2.8	5.7 ± 3.6	8.7 ± 3.0	11.2 ± 4.5	17.0 ± 3.9	20.5 ± 8.3

* Unless otherwise stated, data are the mean and standard deviation of 12 volunteers. Uptake was not determined in those volunteers in whom activity was undetectably low. There was no statistical difference ($p > 0.05$ paired t-test) between rest and exercise studies except where indicated. ND = not determined.

Number of replicates		Statistical probability	
† n = 10	§§ n = 7	¶ $p < 0.05$	‡‡ $p < 0.005$
§ n = 11	** n = 6	‡ $p < 0.01$	†† $p < 0.001$
¶ n = 9	*** n = 3		

to-liver ratios are presented in Table 2. It was often not possible to meaningfully determine these ratios due to the rapid clearance of the background tissue.

Heart uptake was rapid with good retention. The range of percentage injected dose taken up by the heart was 0.6%–1.8% at rest. After exercise, heart uptake was comparable for each individual, range 0.6%–1.7%. The majority of volunteers (9/12 at rest and 10/12 after exercise) had heart uptake exceeding 1.1%. Some clearance was seen from the heart, but there was still appreciable (approximately 1% injected dose) activity in the heart at 2 hr postinjection (range 0.5%–1.5% at rest and 0.7%–1.3% after exercise).

Early liver uptake at rest (4.9%–10.6% of administered dose) fell rapidly to less than 1.6% at 2 hr and, in most subjects, had practically disappeared by 8 hr. After exercise, the initial uptake was about half that at rest and declined at a similar rate, so the majority of subjects showed minimal retention at 4 hr.

Gallbladder activity increased rapidly to peak at about 2 hr. At rest, the individual peak gallbladder activity was up to 10.7% of the injected dose, generally falling to below 1% at 24 hr. After exercise, gallbladder activity followed a similar pattern.

At rest, there was only moderate uptake by the lungs (from 0.7% to 3.0% of the injected dose) initially and this rapidly cleared to almost undetectable levels within 4 hr. After exercise, lung retention was about two-thirds of that at rest.

Substantial activity (4.5% ± 2.2% dose) was observed in the urinary bladder at the first scanning session at rest, whereas there was notably less activity in the corresponding scans after exercise (1.5% ± 1.5% dose, $p < 0.001$).

Salivary glands showed significant initial uptake at rest

TABLE 1
Clinical Characteristics

Patient no.	M/FM	Age (yr)	MI (Y/N)	CABG (Y/N)	EF (%)	# Vess. Dis.	EKG	G/F
1	F	48	Y	Y	18	3	Ant. MI/LVH/RBBB	F
2	M	51	Y	Y	14	2	Ant. MI	G
3	M	46	Y	Y	10	3	Ant. MI/RBBB	F
4	M	52	Y	N	10	3	LVH	G
5	M	41	N	N	4	1	LVH	G
6	F	62	N	N	23	0	LBBB	F
7	M	34	N	N	13	0	Ant. MI	G
8	F	33	N	N	14	0	Ant./Sept. MI/LVH	F
9	F	56	N	N	14	1	LBBB	G

Ant. = anterior; CABG = coronary artery bypass grafting; EF = ejection fraction; F = fasted; G = glucose loaded; Inf. = inferior; LBBB = left bundle branch block; LVH = left ventricular hypertrophy; MI = myocardial infarction; RBBB = right bundle branch block; Sept. = septal; Vess. Dis. = ≥75% stenosis in any epicardial coronary artery.

positioning to obtain the tomographic transmission and emission scans. The collimators were set at 65 mm giving a full width at half maximum (FWHM) resolution of 16 mm. Three transmission planes were acquired for 10 min (two direct planes, one cross-plane) for attenuation correction. Ten millicuries (370 MBq) of $^{13}NH_3$ were administered intravenously and data were acquired for 10 min after 3 min of equilibration. Immediately following the perfusion study acquisition, 10 mCi (370 MBq) of ^{18}FDG were injected intravenously. After a 30 min period for accumulation, emission data were acquired for 10 min. Patients were studied in the fasting state (≥12 hr fasting) (n = 4) or after receiving 50 g of oral glucose (Glucola) 30 min prior to the injection of ^{18}FDG (n = 5).

PET Image Analysis

Perfusion and metabolic PET images were reconstructed, attenuation corrected, and transferred onto a SUN III workstation where a circumferential region of interest (ROI) count density profile was constructed using an interactive program. The initial ROI (containing 21 pixels) was assigned to the intersection of the right ventricular free wall, the interventricular septum and the left ventricular anterior wall at the mid ventricular level (Fig. 1A). Contiguous ROIs of the same size were then placed in a clockwise fashion around the circumference of the perfusion and metabolic PET images. By assigning the first ROI as 0 degrees, the radial angle was automatically computed by the program for the line joining the geometric center of the left ventricular cavity with the center of the ROI. This method of analysis allowed paired data of mean count density of all pixels within a given ROI and radial angle to be generated. The circumferential count density profile for each ROI was then normalized for the ROI with the highest mean count density. In addition, the PET images were interpreted by two experienced observers without benefit of clinical information. The interpretation of either ISCM or NISCM was based on the uniformity of tracer distribution in the myocardium.

Pathology

The hearts were removed at the time of transplantation and placed in phosphate-buffered formalin for approximately 48 hr to allow fixation. A physician from the PET laboratory with the study pathologist oriented the heart in its anatomic position. While viewing the transaxial PET images, they selected a mid-

ventricular transaxial slice corresponding to a PET imaging level. This slice was then divided into eight or nine cross sections which were processed for routine histology. Two paraffin embedded sections were prepared from each tissue block; one was stained with hematoxylin and eosin, the other with a Masson trichrome stain, and the circumferential transmural extent of the infarcted tissue was determined (Figs. 1B–C). Beginning at the same starting point of 0 degrees established in the PET ROI analysis, the percent of noninfarcted tissue was determined by planimetry in each 10-degree sector (Fig. 1B). Histologic myocardial infarction was defined as dense, confluent areas of fibrosis with loss of normal myocardial architecture.

Data Analysis

Pair-wise correlation, using Spearman rank order correlation coefficients (for nonparametric data), was used to correlate normalized ^{18}FDG and $^{13}NH_3$ ROI count density with percent noninfarcted tissue at similar radial locations (±5 degrees) around the circumference of the myocardium.

RESULTS

There were four patients in the ISCM group and five patients in the NISCM group. The average age of the ISCM group was 49 yr (range 46–52) and for the NISCM group 45 yr (range 33–62). All patients in the ISCM group had a history of one or more documented myocardial infarctions and three of four patients had EKG criteria (Q-waves) of myocardial damage. The mean EF was 13% for both the ISCM and NISCM groups (Table 1). No history of prior myocardial infarctions were present in the patients with NISCM, although two patients had anterior precordial Q-waves. All patients with ISCM had significant coronary artery disease pathologically (≥75% stenosis in at least one epicardial coronary artery). None of the five patients with NISCM had angiographic evidence of significant (>75%) coronary artery disease, but two patients had pathologic evidence of significant one-vessel coronary artery disease. Neither of these patients had a totally occluded vessel.

Pathologic examination of all hearts with NISCM revealed no gross or histologic evidence of myocardial in-

TABLE 1
Technetium-99m-Tetrofosmin Human Biodistribution (%Injected Activity, means ± s.d.)*

Organ	5 min	30 min	60 min	120 min	240 min	480 min	24 hr
Heart							
Rest	1.2 ± 0.3	1.2 ± 0.4	1.2 ± 0.4	1.0 ± 0.3	0.7 ± 0.3	0.5 ± 0.2	0.2 ± 0.1†
Exercise	1.3 ± 0.3	1.2 ± 0.2	1.1 ± 0.2	1.0 ± 0.2	0.8 ± 0.2	0.5 ± 0.2	0.3 ± 0.2§
Lung							
Rest	1.7 ± 0.7‡	1.0 ± 0.5§	0.7 ± 0.5**	0.3 ± 0.5	0.1 ± 0.2	ND	ND
Exercise	1.2 ± 0.4	0.7 ± 0.3‡	0.5 ± 0.3**	0.2 ± 0.2**	ND		
Liver							
Rest	7.5 ± 1.7††	4.5 ± 2.1‡‡	2.1 ± 1.0‡‡	0.9 ± 0.6§§	0.3 ± 0.1**¶	0.1 ± 0.2	ND
Exercise	3.2 ± 1.9	2.1 ± 1.0	1.0 ± 0.5†	0.5 ± 0.4§§	0.1 ± 0.1§§	ND	
Gallbladder							
Rest	0.8 ± 1.3	2.9 ± 2.0	5.2 ± 2.4‡	5.3 ± 2.7	4.1 ± 2.3§	4.4 ± 4.1¶	1.5 ± 2.0**
Exercise	0.5 ± 0.6	2.0 ± 1.0	3.0 ± 1.0	3.2 ± 1.0§	2.6 ± 1.6§	3.0 ± 1.9§§	1.1 ± 1.1***
Kidney							
Rest	6.2 ± 2.2	5.1 ± 1.7	4.1 ± 1.7‡	2.9 ± 1.1	1.9 ± 0.7§	1.3 ± 0.5¶	0.8 ± 0.5**
Exercise	4.9 ± 2.2	3.9 ± 2.4	2.8 ± 0.9	2.3 ± 1.0	1.7 ± 0.6§	1.5 ± 0.6§§	0.6 ± 0.4
Salivaries							
Rest	1.5 ± 0.7‡	1.2 ± 0.4‡	1.2 ± 0.5	1.2 ± 0.5	1.2 ± 0.5‡	1.0 ± 0.3	0.5 ± 0.2**
Exercise	0.9 ± 0.1	0.8 ± 0.2	0.9 ± 0.3	0.8 ± 0.2	0.8 ± 0.4	0.5 ± 0.2	0.5 ± 0.3¶
Thyroid							
Rest	0.3 ± 0.2‡	0.3 ± 0.2††	0.2 ± 0.1‡	0.2 ± 0.1¶	0.1 ± 0.2	ND	ND
Exercise	0.2 ± 0.1	0.2 ± 0.1†	0.1 ± 0.1¶	0.1 ± 0.1§§	ND	ND	ND
Gastrointestinal tract							
Rest	2.9 ± 2.3	6.9 ± 3.0¶	10.7 ± 2.7††	13.8 ± 5.0††	19.1 ± 6.2‡	22.6 ± 5.7††	23.6 ± 11.9
Exercise	2.0 ± 1.9	4.4 ± 2.8	5.7 ± 3.6	8.7 ± 3.0	11.2 ± 4.5	17.0 ± 3.9	20.5 ± 8.3

* Unless otherwise stated, data are the mean and standard deviation of 12 volunteers. Uptake was not determined in those volunteers in whom activity was undetectably low. There was no statistical difference ($p > 0.05$ paired t-test) between rest and exercise studies except where indicated. ND = not determined.

Number of replicates		Statistical probability	
† n = 10	§§ n = 7	¶ $p < 0.05$	‡‡ $p < 0.005$
§ n = 11	** n = 6	‡ $p < 0.01$	†† $p < 0.001$
¶ n = 9	*** n = 3		

to-liver ratios are presented in Table 2. It was often not possible to meaningfully determine these ratios due to the rapid clearance of the background tissue.

Heart uptake was rapid with good retention. The range of percentage injected dose taken up by the heart was 0.6%–1.8% at rest. After exercise, heart uptake was comparable for each individual, range 0.6%–1.7%. The majority of volunteers (9/12 at rest and 10/12 after exercise) had heart uptake exceeding 1.1%. Some clearance was seen from the heart, but there was still appreciable (approximately 1% injected dose) activity in the heart at 2 hr postinjection (range 0.5%–1.5% at rest and 0.7%–1.3% after exercise).

Early liver uptake at rest (4.9%–10.6% of administered dose) fell rapidly to less than 1.6% at 2 hr and, in most subjects, had practically disappeared by 8 hr. After exercise, the initial uptake was about half that at rest and

declined at a similar rate, so the majority of subjects showed minimal retention at 4 hr.

Gallbladder activity increased rapidly to peak at about 2 hr. At rest, the individual peak gallbladder activity was up to 10.7% of the injected dose, generally falling to below 1% at 24 hr. After exercise, gallbladder activity followed a similar pattern.

At rest, there was only moderate uptake by the lungs (from 0.7% to 3.0% of the injected dose) initially and this rapidly cleared to almost undetectable levels within 4 hr. After exercise, lung retention was about two-thirds of that at rest.

Substantial activity (4.5% ± 2.2% dose) was observed in the urinary bladder at the first scanning session at rest, whereas there was notably less activity in the corresponding scans after exercise (1.5% ± 1.5% dose, $p < 0.001$).

Salivary glands showed significant initial uptake at rest

TABLE 2
Heart-to-Organ Ratios for ^{99m}Tc-Tetrofosmin*

	Time after injection (min)			
	5	30	60	120
Heart-to-Lung				
Rest	3.1 ± 1.8	4.5 ± 1.5‡	7.3 ± 4.4§	ND
Exercise	4.0 ± 1.1†	5.9 ± 2.2‡	5.9 ± 1.3§	
Heart-to-Liver				
Rest	0.4 ± 0.1¶	0.6 ± 0.3†**	1.2 ± 0.8†††	3.4 ± 2.4‡‡
Exercise	0.8 ± 0.3	1.2 ± 0.7†	3.1 ± 3.0‡	5.0 ± 3.0§

* Unless otherwise stated data are the mean and standard deviation of 12 volunteers. Ratios were not determined in those volunteers where lung (or liver) activity were undetectably low since these would have resulted in unrealistically high ratios. There was no statistical difference (p > 0.05 paired t-test) between rest and exercise studies except where indicated. ND = not determined.

Number of replicates	Statistical probability
† n = 10	†† p < 0.05
‡ n = 8	** p < 0.01
§ n = 6	¶ p < 0.001
‡‡ n = 7	

(0.6%–2.7%), which fell steadily to less than 0.7% at 24 hr. Retention after exercise was significantly lower at most time points up to 8 hr postinjection.

Thyroid uptake, which was initially low at rest (0.1%–0.7%), also fell rapidly so as to be almost undetectable at 4 hr and, again, retention after exercise was lower. Studies performed in rats have indicated that thyroid uptake cannot be blocked by injection of perchlorate. This is taken as an indication that thyroid uptake is not due to free pertechnetate but may represent uptake of the ^{99m}Tc complex itself as has been reported for other cations (14–16).

It was noted that, while there was no significant difference between heart uptake at rest and following exercise, there was a significant reduction in uptake after exercise in all other organ systems (excluding skeletal muscle), amounting to approximately 30% for most but as much as 50% for liver and gallbladder in exercised individuals.

The rapid clearance of ^{99m}Tc-tetrofosmin, roughly equally shared by the urinary and fecal excretory routes, meant that bladder and gastrointestinal tract activity appeared within the first hour after injection. In general, after the first 30–60 min, when bladder activity amounted to a few percent of dose, bladder emptying prior to scanning reduced subsequent bladder activity to relatively low values. However, gastrointestinal tract activity steadily increased to more than 30% in some cases by 48 hr, at which time this was the major contributor to total-body retention and the only activity that could be measured accurately from the 48-hr scan.

Organ Ratios. Heart-to-lung ratios were high (3.1 ± 1.8 at rest, 4.0 ± 1.1 after exercise and at 5 min postinjection) and improved rapidly (Table 2). There was no statistically significant difference between ratios at rest and exercise.

However, it should be noted that data for individuals in whom the ratio exceeded 10 were not considered meaningful and were not included in the analysis.

Heart-to-liver ratios were initially moderate but improved rapidly during the first 2 hr postinjection. As with the lung, ratios exceeding 10 were excluded from the analysis. Ratios from the exercise studies were significantly better than those obtained in resting studies at all times up to 60 min postinjection.

Dosimetry

The results of these calculations for an administered activity of 30 mCi (1110 MBq) ^{99m}Tc-tetrofosmin are presented in Table 3. The effective dose, assuming a 3.5-hr bladder voiding period, is 32.9 × 10^{-3} rad/mCi (8.9 × 10^{-3} mSv/MBq) at rest and 26.7 × 10^{-3} rad/mCi (7.1 × 10^{-3} mSv/MBq) after exercise. The effect of increasing the bladder voiding period from 1 to 4.8 hr is to increase the effective dose by less than 13%.

The organs receiving the highest dose are those of the excretory pathways (gallbladder, lower large intestine (LLI), upper large intestine (ULI), small intestine (SI), urinary bladder and kidney). During exercise the dose to most organs is markedly reduced. Dose to the gonads is estimated to be relatively low at 0.35 rad/30 mCi (3.5 mSv/1110 MBq) to testis both at rest and exercise and, to the ovary, 1.1 rad/30 mCi (10.9 mSv/1110 MBq) at rest and 0.8 rad/30 mCi (7.9 mSv/1110 MBq) after exercise.

Phase II studies with the objective of determining whether it is possible to use ^{99m}Tc-tetrofosmin in the differential diagnosis of reversible myocardial ischemia using a one-day imaging protocol have been performed (17,18). In order for a one-day protocol to be achievable, it was anticipated (given the relatively slow myocardial clearance of the compound) that it would be necessary for the second injection to be three times the activity used in the initial injection. It was assumed that a dose in the range of 8–10 mCi (300–370 MBq) might be necessary for the first injection, which would therefore imply a second injection containing 24–30 mCi (890–1110 MBq). Clinical logistics favor performing the exercise study first. It has been estimated that for an administered activity of 30 mCi (1110 MBq) of ^{99m}Tc-tetrofosmin, the effective dose for the 3.5-hr bladder voiding period would be 1 rad (9.9 mSv) at rest or 0.8 rad (7.9 mSv) after exercise, and the gallbladder wall would receive the highest individual organ dose, in the region of 3.7–5.4 rad (37 to 54 mSv). Similarly, for a 10-mCi (370 MBq) dose the effective dose for rest and exercise would be about 0.3 rad (3.3 and 2.6 mSv, respectively). This implies that a worst case one-day protocol requiring a 10-mCi (370 MBq) (exercise) and 30-mCi (1110 MBq) (rest) injection would result in a total effective dose for the entire study of 1.3 rad (12.5 mSv) and that the gallbladder would receive a dose of about 6.7 rad (67 mSv) for a 40-mCi (1480 MBq) total study. The total body dose for a 30-mCi (1110 MBq) injection is estimated to be 0.4 rad (4 mSv) for either a rest or exercise study.

DISCUSSION

A new drug formulation has recently been developed that yields an injection containing ^{99m}Tc-tetrofosmin on reconstitution with pertechnetate. The simple reconstitution protocol yields the desired ^{99m}Tc complex in high radiochemical purity within 15 min at room temperature. The complex is then stable for 8 hr.

The formulation has been studied in 12 normal human volunteers at doses of up to 87% of the nominal vial contents on two occasions. It was well-tolerated with no serious adverse events reported and no clinically significant drug-related changes detected in any of the vital sign, hematology, blood biochemistry or urinalysis parameters measured.

There may have been some short-term elevations in white cell counts within normal range, apparent within 6 hr of administration but resolved (or resolving) by 48 hr. These changes are not considered to be of clinical significance.

This Phase I study demonstrates the excellent biologic properties of this new ^{99m}Tc-diphosphine complex. Technetium-99m-tetrofosmin shows rapid heart uptake and relatively slow clearance. Background clearance is rapid (from blood, liver and lung). Heart uptake is similar both at rest and exercise, but background clearance is enhanced during exercise studies. The major contributory factor to the improved background clearance after exercise is enhanced sequestration by skeletal muscle. The complex has a high affinity for all muscle tissue as indicated by the uptake in both myocardial and skeletal muscle. It is believed that the enhanced uptake by skeletal muscle during exercise is due simply to a relative increase in the cardiac output to this tissue. Lower uptake by other organ systems is due to less available material resulting from enhanced muscle sequestration and reduced cardiac output to these organs. It remains to be determined whether the enhanced muscle uptake has an additional metabolic component to it. Compared with published data (12) on the currently available ^{99m}Tc cation complex of choice, ^{99m}Tc-sestamibi, ^{99m}Tc-tetrofosmin shows similar heart uptake and retention and blood clearance kinetics but significantly faster clearance from both lung and liver, offering the possibility of earlier imaging or higher quality images at comparable imaging times.

Radiation dosimetry of the agent is favorable when

TABLE 3
Absorbed Radiation Dose Estimates for Various Organs due to ^{99m}Tc-Tetrofosmin Compared with ^{201}Tl and ^{99m}Tc-Sestamibi

Organ	^{201}Tl* rad/2 mCi (mGy/74 MBq)	^{99m}Tc-tetrofosmin Rest	^{99m}Tc-tetrofosmin Exercise	^{99m}Tc-sestamibi* Rest	^{99m}Tc-sestamibi* Exercise
		rad/30 mCi (mGy/1110 MBq)			
Adrenals	0.38 (3.8)	0.46 (4.6)	0.48 (4.8)	0.50 (5.0)	0.49 (4.9)
Brain	—	0.24 (2.4)	0.30 (3.0)	0.12 (1.2)	0.10 (1.0)
Breasts	0.20 (2.0)	0.20 (2.0)	0.25 (2.5)	0.20 (2.0)	0.14 (1.4)
Gallbladder wall	—	5.40 (54.0)	3.69 (36.9)	3.11 (31.1)	3.33 (33.3)
LLI	2.68 (26.8)	2.46 (24.6)	1.70 (17.0)	3.33 (33.3)	2.33 (23.3)
SI	1.20 (12.0)	1.89 (18.9)	1.34 (13.4)	2.44 (24.4)	1.89 (18.9)
Stomach	0.89 (8.9)	0.51 (5.1)	0.51 (5.1)	0.67 (6.7)	0.56 (5.6)
ULI	1.39 (13.9)	3.39 (33.9)	2.24 (22.4)	8.44 (84.4)	6.55 (65.5)
Heart wall	1.67 (16.7)	0.44 (4.4)	0.46 (4.6)	0.81 (8.1)	0.96 (9.6)
Kidney	3.98 (39.8)	1.39 (13.9)	1.16 (11.6)	3.11 (31.1)	2.78 (27.8)
Liver	1.30 (13.0)	0.46 (4.6)	0.36 (3.6)	0.87 (8.7)	0.79 (7.9)
Lungs	0.89 (8.9)	0.23 (2.3)	0.25 (2.5)	0.54 (5.4)	0.58 (5.8)
Muscle	—	0.37 (3.7)	0.39 (3.9)	—	—
Ovaries	0.89 (8.9)	1.06 (10.6)	0.88 (8.8)	1.44 (14.4)	1.11 (11.1)
Pancreas	0.40 (4.0)	0.55 (5.5)	0.56 (5.6)	0.67 (6.7)	0.59 (5.9)
Red marrow	1.30 (13.0)	0.44 (4.4)	0.46 (4.6)	0.39 (3.9)	0.36 (3.6)
Bone surface	2.50 (25.0)	0.62 (6.2)	0.69 (6.9)	0.56 (5.6)	0.49 (4.9)
Salivary glands	—	1.30 (13.0)	0.89 (8.9)	—	—
Skin	—	0.21 (2.1)	0.25 (2.5)	0.18 (1.8)	0.14 (1.4)
Spleen	1.02 (10.2)	0.42 (4.2)	0.46 (4.6)	1.67 (16.7)	1.33 (13.3)
Testes	4.16 (41.6)	0.34 (3.4)	0.38 (3.8)	1.22 (12.2)	1.22 (12.2)
Thymus	—	0.28 (2.8)	0.35 (3.5)	0.24 (2.4)	0.24 (2.4)
Thyroid	1.85 (18.5)	0.65 (6.5)	0.48 (4.8)	2.66 (26.6)	1.89 (18.9)
Bladder wall	0.27 (2.7)	2.14 (21.4)	1.73 (17.3)	0.65 (6.5)	0.53 (5.3)
Uterus	0.37 (3.7)	0.93 (9.3)	0.82 (8.2)	0.90 (9.0)	0.72 (7.2)
Total body	—	0.41 (4.1)	0.42 (4.2)	—	—
Effective dose rem (mSv)	1.57 (15.7)	0.99 (9.9)	0.79 (7.9)	1.33 (13.3)	1.07 (10.7)

* Modified from Leide et al. (19).

compared with that reported for ^{201}Tl (6), allowing in the worst case scenario for ^{99m}Tc-tetrofosmin (i.e. at rest) the administration of up to 20 times the thallium activity for a similar effective dose (Table 3). The more rapid excretion compared with ^{99m}Tc-sestamibi (12) results in a different and in many respects more favorable dosimetry pattern for ^{99m}Tc-tetrofosmin. The doses to gallbladder, brain, red marrow and urinary bladder are elevated as are the doses to breast, bone surface, skin, thymus and uterus after exercise. The doses to all other organs, including ovaries, testes, SI, ULI, LLI, liver, lungs, kidneys, spleen and thyroid, are significantly decreased for ^{99m}Tc-tetrofosmin compared with those reported for ^{99m}Tc-sestamibi (19).

This study indicates that the agent is capable of producing high quality diagnostic images of the heart. It was concluded that the formulation warranted further investigation in patients to determine its value in the diagnosis of ischemic heart disease. The agent has now successfully undergone a Phase II trial to compare one- and two-day imaging protocols for the differential diagnosis of infarct from reversible ischemia in patients with ischemic heart disease (17,18). It is currently in Phase III clinical trials, which compare SPECT and planar imaging for a similar indication.

ACKNOWLEDGMENTS

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