New Technetium-Labeled Myocardial Perfusion Agents

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This article reviews current information on three new ^{99m}Tc-labeled myocardial perfusion agents currently being developed and evaluated.

Key Words: myocardial perfusion imaging; tetrofosmin; furifosmin; NOET

J Nucl Med Technol 1996; 24:119–123

Radionuclide myocardial perfusion imaging in conjunction with exercise or pharmacologic stress testing is an established technique for diagnosing and assessing the severity of coronary artery disease (*1*). Currently ^{201}Tl is the most widely used radiopharmaceutical for myocardial perfusion imaging. Thallium-201, however, has disadvantages such as low photopeak energy (69–83 keV), which can cause decreased image resolution and attenuation by soft tissue. The relatively long half life (73 hr) of ^{201}Tl limits the dose which can be given to the patient, thus reducing the count statistics.

Technetium-99m-labeled radiopharmaceuticals have advantages over ^{201}Tl. Technetium-99m has a higher photopeak energy (140 keV) which will increase image resolution and decrease attenuation. It also has a shorter half-life (6 hr) and a lower radiation dose to the patient which permits a larger amount of radioactivity to be administered, thus increasing the count statistics. Technetium-99m-labeled radiopharmaceuticals can be made in the nuclear medicine laboratory by adding ^{99m}Tc to a prepared kit.

Currently there are two FDA approved ^{99m}Tc-labeled myocardial perfusion agents, sestamibi and teboroxime. Three new ^{99m}Tc-labeled myocardial perfusion agents are undergoing various clinical and experimental trials: tetrofosmin (P-53, PPN1011, Myoview® Amersham Medi-Physics International, Arlington Heights, IL), furifosmin (Q-12, Technicard® Mallinckrodt Medical, St. Louis, MO) and NOET (TcN-NOET CIS Biointernational, Cedex, France). This review will cover current information on all of the three new ^{99m}Tc-labeled myocardial perfusion agents.

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TETROFOSMIN

Background

Tetrofosmin is a newly developed compound of the diphosphine group which forms a lipophilic, cationic complex with technetium. The chemical name of this compound is 1,2-bis [bis 92-ethoxyethyl0 phosphino] ethane. Initial human studies were performed in Europe consisting of 12 healthy male volunteers. After injection of this compound there is rapid clearance from the blood, 5% of the injected dose remains in the blood 10 min postinjection. There is also rapid heart uptake, 1.2% of the injected dose is in the myocardium 5 min postinjection and there is relatively slow clearance from the myocardium. Approximately 1% of the injected dose remains in the myocardium at 2 hr postinjection. Background clearance is rapid and significantly increases following exercise (*2*).

Kit Preparation and Quality Control

Tetrofosmin is supplied as a freeze-dried kit, each kit containing 0.23 mg of tetrofosmin, 0.32 mg of disodium sulphosalicylate, 0.03 mg stannous chloride dihydrate and 1.00 mg of sodium D-gluconate. The vial is reconstituted at room temperature with 4–8 ml of sodium pertechnetate containing no more than 30 mCi of ^{99m}Tc per ml. The vial is shaken to ensure complete dissolution to the lyophilized powder and allowed to stand for 15 min at room temperature. The kit can be used up to 8 hr after reconstitution.

Thin layer chromatography is used to determine radiochemical purity of the tetrofosmin. ITLC/SG strips (Item no. 61885, Gelman Sciences, Ann Arbor, MI) are used. A sample of 10–20 μl is applied to the origin of the strip (Fig. 1). The strip is then placed in an ascending chromatography tank containing a solution of 35:65 acetone/dichloromethane. The strip is removed from the tank once the solvent migrates to the solvent front of the strip. Free pertechnetate migrates to the solvent front (top portion of the strip), bound tetrofosmin to the middle portion, and reduced hydrolyzed ^{99m}Tc and other hydrophilic complexes remain at the origin (bottom of the strip). The percent radiochemical purity is determined by:

$$\frac{\text{Activity in the middle portion of the strip}}{\text{Total activity}} \times 100.$$

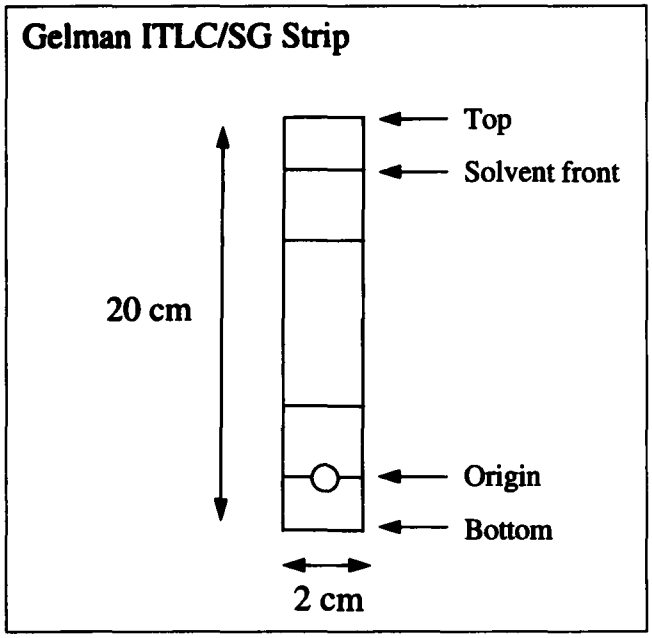

FIGURE 1. Gelman ITLC/SG strip.

Clinical studies can be performed only if the percent bound is >90%.

Myocardial Blood Flow

An experimental study was done to determine if tetrofosmin is a reliable myocardial blood flow tracer. The myocardial uptake and clearance characteristics of tetrofosmin compared to radiolabeled microsphere flow were evaluated in a canine model of ischemia. Six open-chested dogs had complete coronary occlusion of the left anterior descending artery. Two dogs received intravenous adenosine in an incremental fashion (160 μg/kg/min and 320 μg/kg/min) over 18 min. Four dogs received intravenous dipyridamole over 4 min (0.12 mg/kg/min). The dogs were injected with tetrofosmin and radiolabeled microspheres. Myocardial tetrofosmin activity correlated linearly with microsphere flow, r = 0.84 (*3*).

Biokinetics

To determine the biokinetics of tetrofosmin, 20 patients with suspected coronary artery disease underwent a one-day stress and rest study. Serial planar images were acquired at 5–180 min postinjection (Fig. 2). Regions of interest were drawn around the heart, liver, lung, spleen, gallbladder and gastrointestinal tract. Mean decay corrected counts per pixel were plotted against time. On stress images the heart had the highest activity by 15 min, and on rest images delaying 30–45 min allowed for significant organ clearance (*4*). Tetrofosmin appears to remain stable in the myocardium up to 3 hr postinjection (*5*).

Multicenter Trials

A Phase II study was done to determine the optimal protocol for the use of tetrofosmin in the diagnosis of ischemic heart disease. Fifty-five evaluable patients were enrolled at four European centers. All patients underwent an exercise/redistribution planar ^{201}Tl study, followed 3–7 days later by a rest tetrofosmin study, and 1–3 days after that a one-day exercise/rest tetrofosmin study. This imaging protocol validated both a one- and a two-day protocol. There was an 80% concordance between ^{201}Tl studies and the tetrofosmin studies (*6*).

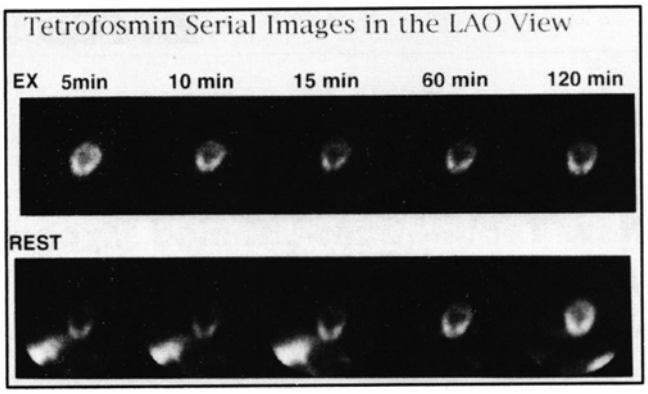

FIGURE 2. Serial images in the left anterior oblique view following exercise (8 mCi) and rest injection (22 mCi) of ^{99m}Tc-tetrofosmin.

The Phase III study was an international, multicenter trial consisting of 10 centers. The aim of the study was to evaluate the use of tetrofosmin in detecting regions of reversible myocardial ischemia in the presence or absence of infarcted myocardium and to obtain further evidence of the safety of tetrofosmin. Patients with suspected coronary artery disease, as determined by an abnormal exercise test, positive ^{201}Tl scan or ≥70% occlusion of a major coronary artery by cardiac catheterization were included in the study. Within two weeks of the ^{201}Tl study patients underwent same-day stress and rest tetrofosmin imaging using two separate injections 4 hr apart. All images were processed at a central core laboratory and interpreted by four experienced readers.

All patients tolerated the injection of tetrofosmin well, there were no drug-related reactions. Technically acceptable paired images were available in 224 of 252 patients enrolled. The tetrofosmin images were of superior quality when compared to the corresponding ^{201}Tl images (Fig. 3). Additionally some patients underwent SPECT imaging which also was of high quality (Fig. 4). Patients were categorized as normal, ischemic, infarction or mixture of ischemia and infarction in each study. Precise concordance for each of the categories in each patient was 59.4%. When categorized as normal or abnormal the concordance between ^{201}Tl and tetrofosmin studies was 80.4% (*7*).

FURIFOSMIN

Background

Furifosmin is a newly developed agent which is a nonreducible cationic, mixed ligand technetium complex. The chemical name of this agent is Trans-(1,2-bis(dihydro-2,25,2-tetramethyl - 3(2H)furanone - 4 - methyleneimino)ethane)bis[tris(3-methoxy-1-propyl)phosphine] ^{99m}Tc(III) (Fig. 5). Studies of the prototypical ^{99m}Tc Q-3 in both animals and humans indicated good clinical potential (*8*). Initial in vitro experiments

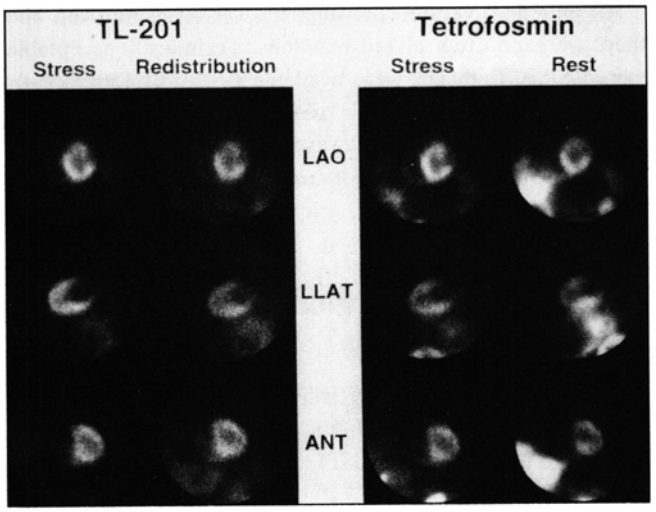

FIGURE 3. Left anterior oblique (LAO), left lateral (LLAT) and anterior (ANT) stress and redistribution ^{201}Tl images with the corresponding stress and rest ^{99m}Tc-tetrofosmin images.

with ^{99m}Tc-furifosmin demonstrated high radiochemical purity and chemical stability. In vivo experiments in rodents showed excellent biodistribution, and no signs of toxicity or adverse reactions (*9*).

Kit Preparation and Quality Control

Furifosmin is prepared by adding 2–3 ml of sterile sodium pertechnetate to the vial containing 20 mg schiff base ligand, 1.5 mg TMPP ligand, 50 mg gamma cyclodextrin, 1.5 mg sodium carbonate and 2.0 mg sodium ascorbate. After swirling the vial it is placed in a boiling bath for 15 min and allowed to cool to room temperature. The kit must be used within 6 hr of reconstitution.

Radiochemical purity is determined by the SepPak® technique. The cartridge is prepared by pushing 10 ml of absolute ethanol through the SepPak, followed by 5 ml of air. The purity is analyzed by applying 10 μl of furifosmin to the cartridge. Then 10 ml of absolute ethanol is slowly pushed through the SepPak cartridge and the eluate is collected in a tube. Next the cartridge is eluted with 10 ml of 0.9% saline followed by 5 ml

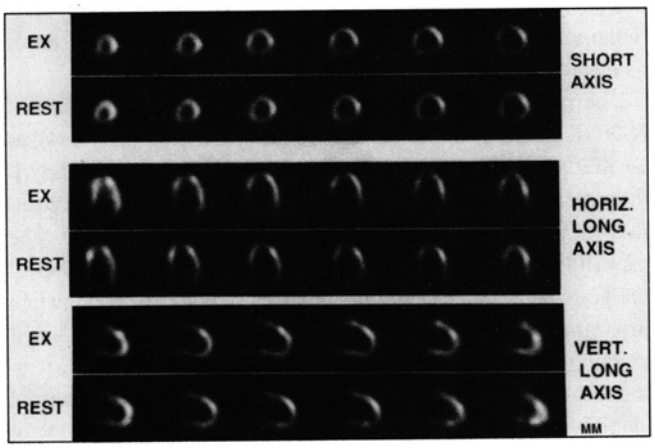

FIGURE 4. Exercise and rest SPECT tetrofosmin study.

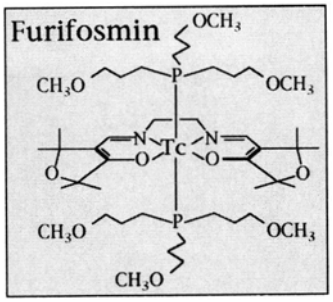

FIGURE 5. Molecular structure of furifosmin.

of air and this eluate is collected in another tube. The SepPak is then placed in a third tube. The three tubes are then counted. The first tube contains the furifosmin complex, the second tube contains the elutable impurities and the third tube contains the nonelutable impurities. The percent radiochemical purity of the furifosmin kit is determined by:

$$\frac{\text{First tube (furifosmin complex)}}{\text{Total activity of 3 tubes}} \times 100.$$

The radiochemical purity must be >90% to perform clinical studies using the kit.

Myocardial Blood Flow

To evaluate myocardial blood flow, seven open-chested dogs were injected with furifosmin and radiolabeled microspheres during pharmacologic stress. Dipyridamole was infused at constant rate over 4 min with a total dose of 0.32 mg/kg in four dogs and 0.56 mg/kg in three dogs. The hearts were excised for well counting of myocardial furifosmin activity and radiolabeled microspheres. Myocardial furifosmin activity correlated linearly with microsphere flow from 0 to 2 ml/gm/min with an r value of 0.88 (*10*).

Biokinetics

The biokinetics of furifosmin were evaluated by imaging 28 normal volunteers and 22 patients with coronary artery disease. Patients underwent a one-day stress and rest furifosmin study. Serial anterior planar images were acquired following both injections. Normal volunteers were imaged at 5, 10, 15, 45 and 60 min and CAD patients were imaged at 5, 10, 45 and 60 min (Fig. 6). Regions of interest were drawn over the heart,

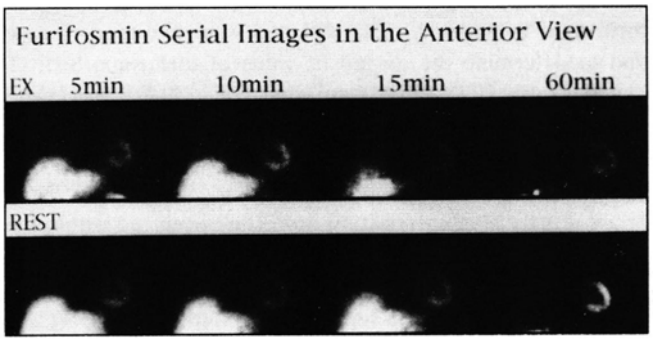

FIGURE 6. Serial images in the anterior view following exercise and rest injection of ^{99m}Tc-furifosmin.

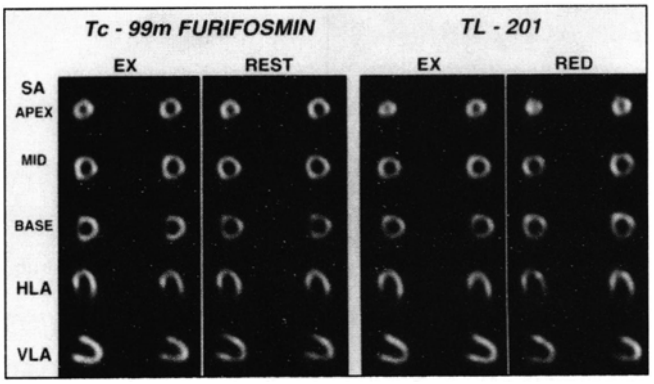

FIGURE 7. Short axis, vertical long axis and horizontal long axis slices. Stress and redistribution ^{201}Tl on the right and the corresponding stress and rest ^{99m}Tc-furifosmin images on the left.

liver, lung and intestine. Decay-corrected counts for each organ were plotted against time. There was similar organ clearance over time in normal volunteers and CAD patients. This suggests imaging can be started early after both stress and rest injection (*11*). The distribution of furifosmin within the heart appears to be stable, with no evidence of myocardial redistribution noted in images acquired for at least 5 hr (*12,13*).

Multicenter Trials

An early study was done in Milan, Italy to characterize the biological behavior of furifosmin in normal human subjects and to evaluate its clinical potential in patients with established coronary artery disease. The normal volunteers received a dose of 10–12 mCi of furifosmin. Antero-posterior images of the upper body were acquired in dynamic mode up to 1 hr postinjection. From these images time-activity curves were calculated for the heart. Twenty patients with coronary artery disease, established by angiography, were selected to undergo imaging. Thirty min postinjection of 20 mCi furifosmin, SPECT images were acquired. None of the patients from either group experienced any adverse reactions that could be attributed to the radiopharmaceutical. In the patients with coronary artery disease furifosmin was distributed according to the patients coronary artery supply. Peak blood activity was reached 2 min postinjection. Furifosmin exhibits rapid heart uptake, approximately 2% of injected dose at rest 1 hr postinjection and 2.6% of injected dose at stress is in the myocardium (*12*). The goals of a multicenter phase III trial were to evaluate the safety of furifosmin in patients with suspected ischemic heart disease and to determine the diagnostic value of furifosmin SPECT imaging with ^{201}Tl SPECT imaging (Fig. 7). Patients were enrolled into the study if they had an unequivocally positive ^{201}Tl study or a clinically high pretest likelihood for coronary artery disease. Patients were excluded if a recent cardiac event or a coronary revascularization procedure occurred within the previous 30 days. Within 2 wk of the ^{201}Tl study patients underwent same day stress (10 mCi) and rest (30 mCi) furifosmin imaging using two separate injections 3–4 hr apart. All images were processed at a central core laboratory and interpreted by three experienced readers.

All patients tolerated the injection of furifosmin well and there were no drug-related reactions. Technically acceptable paired SPECT images were available in 150 of 156 patients enrolled. Agreement for the presence of a perfusion defect between furifosmin and ^{201}Tl was 86%. The exact concordance for the diagnostic categories of normal, ischemic, scar or mixed defect was 67.3% (*13*).

NITRIDO DITHIOCARBAMATE

Background

Technetium-99m-N-NOET is a new neutral lipophilic myocardial imaging agent bis (N-ethoxy N-ethyl dithiocardarnate) nitrido ^{99m}Tc (^{99m}Tc-N-NOET) and has shown high myocardial uptake in various animal studies (*14*).

Kit Preparation and Quality Control

Technetium-99m-N-NOET is prepared from a kit using a two-step process. Fifty mCi of sodium pertechnetate is added to a vial containing 3.0 mg of tris(m-sulfophenyl)phosphine, [P(m-C6H4SO3)3]Na3) (TPPS) and 1.0 mg of N-methyl, S-methyl dithiocarbazate [H2N-N(CH3)-C(=S)SCH3, (DTCZ) dissolved in 1 ml of 0.1M HCl. The solution is heated at 100°C for 15 min and allowed to cool to room temperature. The pH is raised to 8.0 by adding 1.0 ml of sodium phosphate buffer and 1.0 ml of an aqueous solution containing 10.0 mg of the sodium salt of N-ethoxy, N-ethyl dithiocarbamate (NOET) (*14,15*).

Radiochemical purity is determined by thin layer chromatography. A 2.5 cm × 15 cm silica gel strip (Scheicher and Schull, Keene, NH) is eluted using an ascending chromatography tank containing dichloromethane. Free pertechnetate and unreacted ^{99m}Tc-N will remain at the origin and ^{99m}Tc-N-NOET complex migrates to the middle of the strip (*14,15*).

Myocardial Blood Flow

An experimental study was done to compare the myocardial distribution of ^{99m}Tc-N-NOET with regional myocardial blood flow in dogs after permanent and temporary partial coronary occlusion, with and without infusion of dipyridamole. Myocardial uptake of ^{99m}Tc-N-NOET was measured at different times to evaluate potential redistribution of this agent.

There was a linear correlation between myocardial ^{99m}Tc-N-NOET activity and mircosphere flow at 15 min ($r = 0.94$), at 15 min with dipyridamole ($r = 0.94$), at 90 min with dipyridamole ($r = 0.91$) and when arterial occlusion was discontinued there was no longer a linear correlation ($r = 0.26$). The experiment demonstrated that up to 90 min after injection of ^{99m}Tc-N-NOET there was an excellent relationship between myocardial retention of this agent and blood flow. Almost complete redistribution of this agent occurs 90 min after injection of ^{99m}Tc-N-NOET. This agent may be a myocardial viability tracer and a potential technetium compound analog of ^{201}Tl (*16*).

Multicenter Study

To assess the clinical value of ^{99m}Tc-N-NOET in the diagnosis of coronary artery disease, 25 patients undergoing cardiac catheterization had stress, redistribution and reinjection ^{201}Tl SPECT imaging. Following this study the same patients underwent a stress, delayed and 4-hr postinjection SPECT ^{99m}Tc-N-NOET study. The patients were injected with 15 mCi ^{99m}Tc-N-NOET at peak exercise and stress imaging was begun 30 min postinjection. Nineteen patients had coronary stenosis ≥50% and 6 were normal. The overall sensitivity for the detection of coronary artery disease was 74% with ^{99m}Tc-N-NOET imaging and the specificity was 100%. In segmental analysis between ^{99m}Tc-N-NOET and ^{201}Tl SPECT imaging there was good agreement between normal versus abnormal perfusion with a concordance of 94% (*15*).

CONCLUSION

Tetrofosmin, furifosmin and NOET are promising new myocardial perfusion agents. Tetrofosmin and furifosmin organ biokinetics suggest that imaging can be started soon after stress and rest injection which allows for a flexible imaging protocol. Preliminary data on NOET suggest that this agent is a potential technetium compound analog of ^{201}Tl.

ACKNOWLEDGMENTS

The author thanks Donna Natale and the Yale University Radionuclide Core Laboratory for their assistance in the preparation of the myocardial perfusion images.

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