Technetium-99m-Teboroxime: A New Agent for Myocardial Perfusion Imaging

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This is the first article in a four-part series on new radiopharmaceuticals. Upon completion of this article, the nuclear medicine technologist will be able to: (1) understand the important aspects of this technetium-99m-labeled myocardial perfusion agent, and (2) identify important imaging parameters.

The assessment of myocardial perfusion by nuclear scintigraphy is an important diagnostic tool for the evaluation of patients with ischemic heart disease. Although a variety of radiopharmaceuticals have been used to assess coronary blood flow, thallium-201 (^{201}Tl) has become the most commonly used imaging agent since its introduction for clinical use by Lebowitz et al. in 1973 (*1*).

Thallium-201 does, however, demonstrate several drawbacks that makes it less than ideal for imaging. Cyclotron production limits its availability and increases its cost. The physical properties of ^{201}Tl are not ideal for Anger camera scintigraphy. It has a low-energy photopeak (68–80 keV mercury-201 X-ray) which results in soft tissue attenuation artifacts. Its relatively long half-life (73 hr) limits the activity amount that may be administered, which results in a low photon flux. The low administered activity also results in prolonged imaging times. Myocardial perfusion imaging currently relies on redistribution after a single stress injection to assess resting perfusion. However, recent studies suggest that a second rest injection may be needed to obtain a true resting perfusion image (*2*).

Technetium-99m (^{99m}Tc) has physical properties that are ideal for Anger camera imaging. It is readily available from an on-site generator, is inexpensive, has a short half-life (6 hr), and emits a photopeak (140 keV) with an optimal energy for imaging. Due to its favorable radiation dosimetry, higher activity amounts of ^{99m}Tc can be administered, which may allow for a significant reduction in the time necessary for data acquisition.

For reasons such as these, many researchers have worked toward the development of a new ^{99m}Tc-labeled myocardial perfusion agent. The ideal ^{99m}Tc-labeled agent should include properties such as rapid blood-pool clearance, high myocardial extraction with rapid myocardial uptake, and high target-to-nontarget ratios.

Among the several new ^{99m}Tc-labeled compounds that have been developed for myocardial perfusion imaging (*3–6*) is technetium-99m-teboroxime.* Initial animal and human studies demonstrate that this compound displays a high degree of myocardial extraction and a short myocardial residence time. High quality diagnostic images can be obtained with a combined stress and rest study within 1 to 1.5 hr. Imaging can be performed using either planar or single-photon emission computed tomography (SPECT) acquisition. Hepatic uptake of teboroxime can preclude visualization of the inferior wall in some views, but does not appear to affect diagnostic results. The purpose of this article is to familiarize the reader with the technical and clinical details of teboroxime myocardial imaging.

BACKGROUND

Teboroxime is a small, neutral, lipophilic agent that has been derived from a class of compounds known as boronic acid adducts of technetium dioxime complexes (BATOs) (*7*). Pre-clinical testing in rats with ^{99m}Tc-teboroxime demonstrated that the compound was rapidly cleared from the bloodstream, with the liver serving as the main organ of excretion (*7*). Imaging studies in dogs showed that the myocardium could be visualized and imaged from 2–20 min postinjection (*8*). The tracer showed rapid lung clearance with peak activity occurring in the liver 4.5–7 min postinjection. Areas of infarction could be clearly seen in all 13 canine infarct models studied. Using an isolated blood-perfused rabbit heart model, Leppo et al. found that ^{99m}Tc-teboroxime has high myocardial extraction over a wide range of coronary blood flow (*9*).

In preliminary human clinical studies, the myocardium was visualized and imaged from 60 sec through 20 min postinjection (*7*). The compound also demonstrates a short myocardial retention time with a biexponential pattern of myocardial clearance (*10*). Myocardial clearance half-times are 2 min (68%) and 78 min (32%). Due to its short residence time in the myocardium, two separate injections are necessary for a stress and rest perfusion study. The washout pattern of ^{99m}Tc-

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teboroxime shows that ~10% of the compound remains in circulation after 10 min. The estimated absorbed radiation doses to organs and tissues from an intravenous injection of ^{99m}Tc-teboroxime are shown in Table 1. This table demonstrates that the gallbladder wall and small and large intestines are the target organs.

As part of a Phase II clinical study, Seldin et al. (*5*) compared planar myocardial perfusion imaging using ^{201}Tl and ^{99m}Tc-teboroxime in normal volunteers and in patients with documented coronary artery disease (CAD). All of the perfusion images on the normal volunteers using either ^{201}Tl or ^{99m}Tc-teboroxime were interpreted as normal. In the group of CAD patients studied, both tests demonstrated equivalent sensitivity in identifying CAD (^{201}Tl—85%, ^{99m}Tc-teboroxime—80%, p = ns), and in the identification of abnormal vessels (^{201}Tl—47%, ^{99m}Tc-teboroxime—42%, p = ns). Both agents gave false-positive results in the identification of 1 out of 15 abnormal vessels. In 14 out of 20 ^{99m}Tc-teboroxime scans, inferoapical segments were obscured due to hepatic uptake of the tracer. This uptake did not interfere with abnormal vessel identification, however, since these segments could be seen in multiple views.

Because initial clinical experience with ^{99m}Tc-teboroxime, including this study, demonstrated favorable kinetics, imaging, and safety of the compound, a multicenter evaluation was performed.

A Phase II/III multicenter clinical trial of ^{99m}Tc-teboroxime was undertaken at eight investigational sites (*11*). One hundred and ninety-four subjects were studied at maximal stress and rest. Each subject received two separate injections of ^{99m}Tc-teboroxime ranging from 12–40 mCi. Rest studies were performed 1.5–2.5 hr after stress studies. In some cases the rest study was performed first, with the stress study following within 1 hr.

TABLE 1. Radiation Dose Estimates of Teboroxime (Gallbladder Emptying Interval of 6 Hours)*

Organ	Absorbed Dose		
	rads/mCi	rads/15 mCi	rads/30 mCi
Brain	0.0136	0.20	0.41
Gallbladder wall	0.1320	1.98	3.96
SI	0.0718	1.08	2.15
ULI	0.1270	1.91	3.81
LLI	0.0908	1.36	2.72
Heart wall	0.0229	0.34	0.69
Kidneys	0.0244	0.37	0.73
Liver	0.0646	0.97	1.94
Lungs	0.0304	0.46	0.91
Spleen	0.0191	0.29	0.57
Thyroid	0.0146	0.22	0.44
Ovaries	0.0404	0.61	1.21
Testes	0.0137	0.21	0.41
Red marrow	0.0205	0.31	0.62
Urinary bladder	0.0252	0.38	0.76
Total body	0.0201	0.30	0.60

* 2-hr urinary bladder voiding interval (Table obtained courtesy of Squibb Diagnostics).

When compared with the overall clinical impression (based on ^{201}Tl and/or coronary angiography), myocardial perfusion imaging with ^{99m}Tc-teboroxime demonstrated a sensitivity of 83.2% and a specificity of 92.1%. Technetium-99m-teboroxime imaging agreed with ^{201}Tl imaging in 90.4% of the studies and with coronary angiography in 76.2% of the studies. No adverse effects attributable to ^{99m}Tc-teboroxime were reported.

PREPARATION AND LABELING

The preparation of ^{99m}Tc-teboroxime does not differ substantially from techniques involved in preparing other ^{99m}Tc-labeled agents. Teboroxime is supplied as a single vial kit in a lyophilized (freeze-dried) form. Using an aseptic technique, the vial is reconsituted by adding up to 100 mCi of sterile, pyrogen-free [^{99m}Tc] pertechnetate contained in 1 ml. To obtain the appropriate volume, it may be necessary to dilute the ^{99m}Tc with preservative-free sodium chloride injection (0.9% NaCl). During reconstitution, it is important that air is not added to the nitrogen atmosphere of the vial. Injected air will cause oxidation, thereby reducing the radiochemical purity of the compound. It is also important that the vial remain upright, preventing contact of the product with the rubber stopper. After reconstitution, the vial is gently swirled then heated upright in a water bath or heating block for 15 min at 100°C. The use of a heating block is recommended for convenience and to ensure that the vial remains upright. A water bath may be used if care is taken to assure that the vial is held in place.

After the solution cools to room temperature, paper chromatography is performed to measure the fractions of free pertechnetate and reduced hydrolyzed ^{99m}Tc. The chromatography procedure requires ~10–15 min to develop. Two strips of Whatman 31 ET paper measuring 1.3 cm × 11 cm are spotted with one drop of the preparation. One strip is developed in normal saline to determine the percentage of free pertechnetate, and the other in a 1:1 solution of normal saline/acetone to determine the percentage of reduced hydrolyzed ^{99m}Tc (see Fig. 1). Enclosing the strips in tape after the

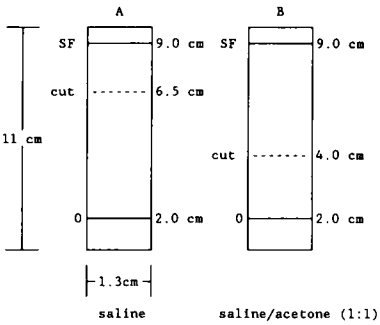

FIG. 1. Instant thin-layer paper chromatography method using Whatman 31ET paper; O = origin, SF = solvent front. % free pertechnetate (A) = (SF/SF + O) × 100. % reduced hydrolyzed ^{99m}Tc (B) = (O/O + SF) × 100.

development will ease handling and minimize the risk of contamination. Each segment can be rolled-up and placed in a test tube for counting.

The sum of the percentage of free pertechnetate and percentage of reduced hydrolyzed ^{99m}Tc in the prepared compound must be <10% for the product to be released for patient administration. The prepared ^{99m}Tc-teboroxime should be stored at room temperature in the original glass vial and be used within 6 hr of preparation. The recommended single dose of ^{99m}Tc-teboroxime is 10–40 mCi, with a total dose for the combined stress and rest studies of less than 60 mCi.

PLANAR IMAGING

Static or dynamic planar imaging can be performed for a ^{99m}Tc-teboroxime myocardial perfusion study. Stress or rest scans may be completed in any sequence. Utilizing either treadmill or bicycle exercise, patients are injected with 10–40 mCi of ^{99m}Tc-teboroxime at peak exercise with exercise continued for an additional 30–60 sec following injection. Ideally, imaging should begin within 2 min of injection. Electrocardiogram leads V1–V6 should be removed prior to image acquisition, while limb leads can remain in place for continued monitoring. Positioning the patient upright during image acquisition is helpful in minimizing hepatic activity and improving image quality.

Several different imaging protocols have been performed for planar imaging. Seldin et al. (*5*) utilized an upright bicycle exercise protocol. Upright imaging began 2 min after injection of 15 mCi of ^{99m}Tc-teboroxime. Dynamic 128 × 128 matrix acquisition began in the anterior view at 10 sec/frame at the time of injection and continued for 5 min. The camera was then repositioned into a 30° left anterior oblique (LAO) view with a 6-min dynamic acquisition, and lastly into a 60° LAO view with a 9-min dynamic acquisition. The time interval between each view was 30 sec. Approximately 2 hr later, a second 15-mCi dose of ^{99m}Tc-teboroxime was administered at rest followed by the same imaging protocol. The dynamic images were summed, excluding the initial 2 min of blood pool in the anterior view, yielding an anterior, 30° LAO, and 60° LAO view.

An alternate method of planar imaging, as performed at our institution, involves upright patient positioning for stress and rest studies. Following a symptom-limited Bruce protocol exercise treadmill test, 12–20 mCi of ^{99m}Tc-teboroxime is injected upon maximal exertion. Patients are then quickly positioned in front of the gamma camera in either a seated or standing position within 1 min of completion of the exercise. Images are acquired in either dynamic or static collection mode using a low-energy all-purpose (LEAP) collimator. Dynamic acquisition is performed in a 128 × 128 pixel matrix with a frame rate of 20 sec per frame. Imaging is begun in the anterior view with collection of 2–4 frames after clearance of blood-pool activity. The patient is then rotated to a 45° LAO view with 2–4 frames of acquisition, and then to a 70° or left lateral (LLAT) position for an additional 2–4 frames. The time interval between each view is equivalent to 1 frame or 20 sec. The total time for imaging is generally less than 5 min. A second set of stress images is then obtained to assess early differential washout. Approximately 1 hr after exercise injection, the patient returns for a rest study. A single 60-sec static anterior image is acquired prior to the rest injection to demonstrate absence of residual myocardial activity. The patient then receives an additional 12–20 mCi of ^{99m}Tc-teboroxime followed by the same imaging protocol. The dynamic images are summed using two to three frames for each view. The repositioning or movement frames are excluded from analysis.

Static acquisition is performed in a 128 × 128 pixel matrix with a collection time ~ 45–60 sec for each stress image, and ~ 30–45 sec for each rest image. The time per view may vary due to counting statistics. Counts of at least 300K per view are desirable. The static mode of acquisition eliminates computer manipulation involved in summating views in the dynamic protocol.

In either acquisition mode, dynamic or static, the order of stress/rest may be reversed. In studies where rest precedes stress, the second injection can still be administered within 1 hr after the first injection.

SPECT IMAGING

With advances in gantry and detector hardware and sophisticated software, the use of SPECT has become an increasingly popular alternative to planar imaging. SPECT images of the myocardium may be acquired over a 180° or 360° angular rotation. Computer reconstruction is performed to demonstrate a representative three-dimensional cross-section of the myocardium. In some instances, SPECT imaging may be superior to planar imaging.

While most of the clinical ^{99m}Tc-teboroxime imaging studies have utilized planar imaging protocols, SPECT imaging has been performed and is clearly feasible (*12–13*).

One method of SPECT acquisition, as performed at the University of Texas Medical School at Houston (*12*), consists of a 180° acquisition, following stress and rest injections. Imaging is acquired using a LEAP collimator with the camera set for 32 steps at 15 sec/step. The patient is imaged following a 20 mCi injection of ^{99m}Tc-teboroxime at peak exercise and again 90 min later at rest. Reconstruction is performed with a 64 × 64 matrix using a Hanning filter with a 0.83 Hz cutoff.

Bellinger et al. (*13*) injected patients with 10 mCi of ^{99m}Tc-teboroxime at maximal exercise and then began imaging within 90 sec from the time of injection. SPECT was performed over a 180° non-continuous rotation using a general purpose collimator with the camera set for 32 steps at 15 sec/step. A 64 × 64 zoomed matrix was used and total imaging time was 10 min. Approximately 90 min after stress injection, the patient was given an additional 30 mCi of ^{99m}Tc-teboroxime and imaging was repeated. Reconstruction was performed with a Butterworth filter and a preprocessing scaling program was used to equalize counts over the myocardium between rest and stress images.

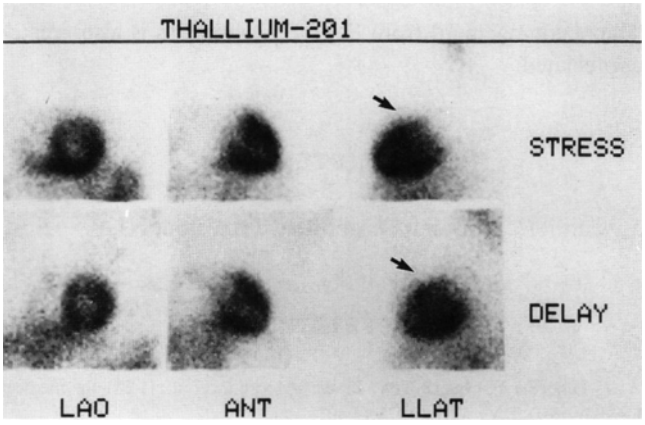

FIG. 2. Thallium-201 stress and redistribution scan in the left anterior oblique (LAO), anterior (ANT), and left lateral (LLAT) projections.

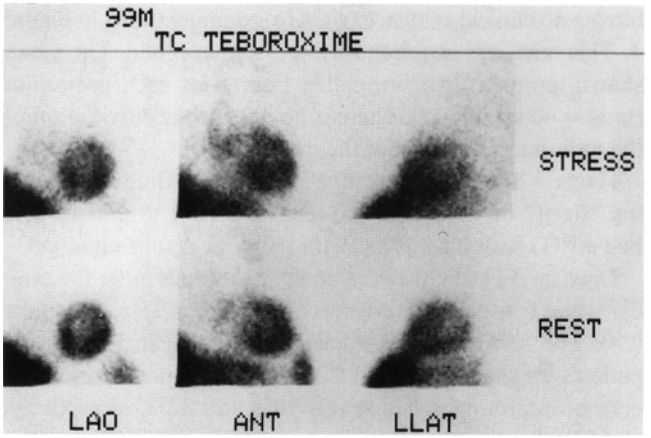

FIG. 4. Technetium-99m-teboroxime stress and rest scan. Normal distribution of the tracer is demonstrated.

IMAGING CONSIDERATIONS

Several steps should be taken into account prior to initiation of a ^{99m}Tc-teboroxime scan. Since teboroxime displays such a short retention time in the myocardium, it is crucial that imaging begin within 2 min postinjection (if a lengthy delay occurs, the study may be incomplete due to uninterpretable images). Accordingly, the ideal location for the exercise equipment and the imaging camera is in the same room. The position of the camera and the specific data acquisition parameters should be determined and set prior to the study. It is also very helpful to rehearse the protocol with the patient before imaging to prevent an unnecessary delay. For SPECT scans, lasers may be helpful in pre-positioning the patient for precise data acquisition.

Hepatic uptake of ^{99m}Tc-teboroxime poses a potential problem from an imaging standpoint; therefore upright patient positioning for scanning is advantageous. An upright position helps minimize hepatic interference with the inferior wall of the myocardium and also allows for rapid patient positioning. Since hepatic activity of the tracer is initially low, but is dominant by 5–10 min postinjection (*5*), it may also be advantageous to acquire the LAO 70° (or LLAT) view first. It is in this projection that hepatic activity is most pronounced in obscuring visualization of the inferior wall.

CLINICAL CASES

As part of the Phase II/III multicenter clinical trial, we have performed planar imaging with ^{99m}Tc-teboroxime in over 80 patients at our institution. The patient population consisted of 65 males and 15 females (mean age ± s.d., 58 ± 11 yr). All patients had undergone cardiac catheterization or exercise ^{201}Tl testing within 3 mo. Informed consent was obtained from each patient prior to study enrollment.

Representative ^{99m}Tc-teboroxime images are shown in Figs. 3–5. All images are displayed as raw data, with no computer smoothing or processing applied. Figures 2 and 3 demonstrate representative ^{201}Tl and ^{99m}Tc-teboroxime images performed within 1 wk apart on the same patient. Except for the increased hepatic uptake in the ^{99m}Tc-teboroxime scan, the studies are very comparable. Both scans demonstrate normal perfusion patterns. A soft tissue artifact (due to breast attenuation) is seen on the anterior wall in the LLAT views.

A normal ^{99m}Tc-teboroxime scan performed on a patient

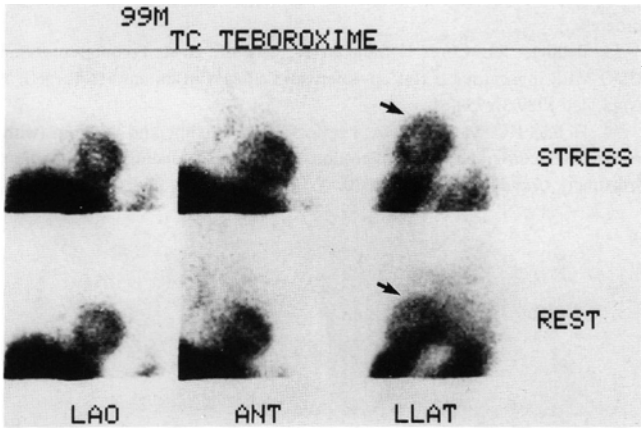

FIG. 3. Technetium-99m-teboroxime stress and rest scan in the LAO, ANT, and LLAT projections. Note the presence of significant hepatic activity.

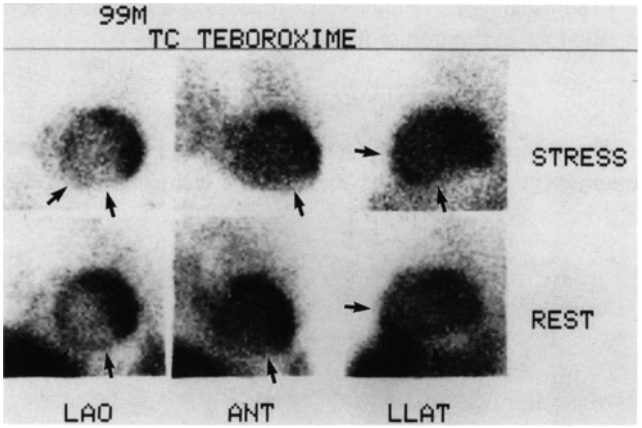

FIG. 5. Technetium-99m-teboroxime stress and rest scan. Large areas of "fixed" defects are present in the anterior, anterolateral, septal, apical, inferior and posterior walls of the left ventricle.

having no clinical evidence of CAD is demonstrated in Figure 4. This scan was acquired in the dynamic mode. The views shown represent two summated frames for each projection (total = 40 sec/image). There is homogeneous distribution of the radiotracer throughout the myocardium.

Figure 5 represents a positive ^{99m}Tc-teboroxime scan showing "fixed" or non-stress induced defects. The patient also had a ^{201}Tl scan 2 wk prior, with the same results obtained.

Data on 54 patients were analyzed to determine the concordance between ^{99m}Tc-teboroxime and ^{201}Tl scintigraphy (*14*). The two modalities were in agreement in 91% of the patients for the detection of CAD. Concordance for the presence of infarct or ischemia was 70% and 82%, respectively. Overall, there was excellent correlation between ^{99m}Tc-teboroxime and ^{201}Tl imaging for the diagnosis of normal or abnormal myocardial perfusion.

DISCUSSION

While ^{201}Tl remains the most common method of choice for myocardial perfusion imaging, ^{99m}Tc-teboroxime may offer several advantages. The rapid degree of tracer washout from the myocardium allows administration of a second injection within 60–90 min of the first, which permits an entire stress/rest or rest/stress study to be completed within 1 to 1.5 hr. A comparable ^{201}Tl stress/redistribution study takes ~ 3–4 hr (or longer) to complete. Therefore, the time required for completion of a ^{201}Tl scan can be reduced by more than half. Rapid perfusion imaging with ^{99m}Tc-teboroxime increases patient convenience due to the shorter imaging time and greater scheduling flexibility. Since teboroxime is labeled to ^{99m}Tc, which is readily available, doses can be prepared as needed. This eliminates the need to order doses in advance from an outside manufacturer.

Due to the rapid myocardial washout of ^{99m}Tc-teboroxime, imaging must be completed within 5–10 min. This requires special attention to the imaging protocol by the technologist so that scanning can be completed without delay. It is also important that the exercise and scanning equipment be in close proximity. Upright patient positioning is recommended to minimize hepatic interference with the inferior wall.

In summary, ^{99m}Tc-teboroxime imaging is a promising new method for evaluation of myocardial perfusion.

ACKNOWLEDGMENTS

The author thanks Seth Dahlberg, MD for his review of the manuscript and Stephanie Roy for her technical assistance. The encouragement from Squibb Diagnostics is also greatly appreciated.

NOTES

*Cardiotec®, Squibb Diagnostics, Princeton, NJ.

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