FDA Approves Two New Technetium-Labeled Cardiac Agents and a Pharmacologic Alternative to Exercise in Stress-Thallium Studies

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IN DECEMBER 1991, THE U.S. Food and Drug Administration (FDA) approved the use of two new technetium-99m(^{99m}Tc)-based myocardial perfusion imaging agents, ^{99m}Tc-teboroxime [CardioTec® , Squibb Diagnostics, Princeton, New Jersey], ^{99m}Tc-sestamibi [Cardiolite® , Du Pont Merck Pharmaceuticals, North Billerica, Massachusetts], and dipyridamole USP [I.V. Persantine® , Du Pont Merck], a drug that provides an alternative to exercise in stress-thallium studies in patients who are incapable of performing exercise.

The new agents harbinger a resurgence of interest in myocardial perfusion studies, and promise significant advancements in the evaluation and diagnosis of cardiac ailments, says Robert C. Hendel, MD, assistant professor of medicine, sections of cardiology and critical care, Northwestern Medical School, and associate director of medical intensive care, Northwestern Memorial Hospital, Chicago, Illinois. Developed as alternatives to thallium as a tracer in myocardial perfusion imaging studies, the two ^{99m}Tc-labeled agents underwent years of extensive clinical trials worldwide prior to their approval in the United States. With the availability of the third product, I.V. Persantine, says Edward Geltman, MD, Washington University School of Medicine, St. Louis, Missouri, "we now have the capability of evaluating a much larger population of patients and determining their risk of coronary artery disease (CAD) in order to prepare proper therapy."

Although myocardial perfusion imaging with the cationic tracer thallium-201 (^{201}Tl) has been the established standard in the diagnosis of myocardial infarction and detection of CAD for over a decade, ^{201}Tl remains a less than ideal perfusion imaging agent, primarily because it is cyclotron-produced rather than generator-produced (thereby limiting its availability and supply). In addition, ^{201}Tl has a relatively low photon energy (69 to 83 keV), which allows for considerable attenuation. Its relatively long half-life (73 hours) limits the injected dose to 3-4 mCi, resulting in low count density and variable image quality, and restricts the ability to perform sequential imaging, according to Dr. Hendel. "It's difficult to do emergency studies with thallium because images must be collected before the agent begins to wash out of the heart, usually within 15 minutes," says Daniel S. Berman, MD, professor of medicine, UCLA School of Medicine, director of nuclear cardiology, Cedars-Sinai Medical Center, Los Angeles, California. "Imaging within this time frame is difficult because in many cases the patient has not been stabilized."

Technetium-Labeled Cardiac Agents

The technetium-99m-labeled agents, Cardiolite and CardioTec, provide a way around some of the difficulties associated with thallium. Comments Frans J. Wackers, MD, professor of diagnostic radiology and medicine, Yale University School of Medicine, New Haven, Connecticut, "Technetium-labeled agents have essential advantages over thallium-201. Technetium-99m-labeled agents provide better radiation dosimetry, allowing for the injection of a higher dose, which produces higher image quality, increased confidence of image interpretation, and higher resolution imaging, which provides for the possibility of correction for attenuation and scatter that might image artifacts." Says Jamshid Maddahi, MD, director, clinical PET center, UCLA School of Medicine, Los Angeles, California, "Technetium-99m-labeled agents also provide the possibility of performing first-pass evaluation of ventricular function, and gated acquisition for assessing regional wall motion and thickening." Another advantage of technetium-99m-labeled agents is that they are more conveniently prepared and readily available from a generator. "Unlike thallium, which must be ordered from an outside source in advance of an imaging procedure, [^{99m}Tc]teboroxime and [^{99m}Tc]sestamibi can be easily prepared on site as needed," notes Dr. Maddahi.

CardioTec, a kit for the preparation of ^{99m}Tc-teboroxime, and Cardiolite, the cationic technetium complex ^{99m}Tc-sestamibi, allow physicians to rapidly evaluate areas of ischemic or infarcted myocardial tissue in patients with known

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or suspected CAD. Each agent has its proponents.

Jeffrey A. Leppo, MD, director of nuclear cardiology, University of Massachusetts Medical Center, Worcester, Massachusetts, elaborates on what he sees as the two major advantages of the teboroxime agent over thallium in myocardial perfusion imaging: "[The agent's] transport characteristics, specifically its high extraction and capillary flux, allow the agent to be rapidly sequestered in the myocardium and are well suited to clinical studies. And, once again, due to the higher photon energy levels of technetium, ^{99m}Tc-teboroxime produces images of a superior quality — and it accomplishes this in about half the time as a thallium study."

The same is said of ^{99m}Tc-sestamibi. "The image quality provided by ^{99m}Tc-sestamibi studies are uniformly superior to those generated by thallium studies," says Warren H. Moore, MD, chief of nuclear medicine service, St. Luke's Episcopal Hospital, Texas Children's Hospital, Texas Heart Institute, Houston, Texas. "This presents the potential for greater diagnostic accuracy." Clinical trials have indicated that ^{99m}Tc-sestamibi can accurately identify the presence of myocardial infarction damage to the anterior and inferior/posterior heart walls.

Unlike the sestamibi agent, technetium-99m-teboroxime demonstrates rapid clearance from the myocardium. The teboroxime agent is one of the neutral, lipophilic, technetium-containing complexes called BATOs [boronic acid adducts of technetium dioximes]. According to Dr. Maddahi, BATO compounds readily cross the cell membrane, including those of the myocardium. "Thus, ^{99m}Tc-teboroxime accumulates in normal oxygenated heart tissue," he says, "but is excluded from damaged or dead tissue. Subsequently, ^{99m}Tc-teboroxime is efficiently extracted by the myocardium, even at the high flow rates that are common during patient exercise or pharmacologic intervention." The rapid clearance of the tracer also allows the physician to quickly re-image the patients with a second injection—unlike other agents which typically require that rest and stress images be obtained at least several hours apart.

"The rapid and efficient extraction and rapid washout are necessary to accurately assess myocardial perfusion, especially with the high myocardial flow rates associated with patient exercise and pharmacologic stress," says Dr. Hendel. "Once the patient reaches maximum heart rate during the stress segment of the examination, the image can be taken within two minutes of the injection, permitting physicians to evaluate CAD more quickly." Says Raye Bellinger, MD, director, Cardiac Catheterization Laboratory and Center for Cardiovascular Research, David Grant USAF Medical Center, Travis Air Force Base, Fairfield, California, "We can perform a complete rest-stress study in less than two hours with only 20 minutes of total camera time, compared to the four hours—including 50 minutes of total camera time—needed for thallium scans." The quickness of a complete diagnostic rest-stress study afforded with ^{99m}Tc-teboroxime, "will probably find high patient approval," wrote Lynne L. Johnson, MD, director of nuclear cardiology laboratory, professor of medicine, Columbia University, New York, in the October 16, 1990 issue of *The American Journal of Cardiology,* "and offer the opportunity to acquire function and regional perfusion data in a single procedure, which will add important diagnostic and prognostic information to the study."

Dr. Leppo cautions that, "because of its extremely fast myocardial extraction and washout, the imaging procedure with ^{99m}Tc-teboroxime is more technically challenging, since the staff has to rapidly image the patient in short period of time—usually less than fifteen minutes. Furthermore, the quick washout demands that the imaging camera has to be situated in close proximity to the exercise apparatus. Thus, the accelerated pace of the study requires more efficiency on the part of the technologists and physicians. This can be seen as either a disadvantage or an advantage." Dr. Leppo maintains that the speed of the imaging procedure is the only salient advantage of ^{99m}Tc-teboroxime studies versus thallium studies. "We cannot yet conclude that the quality of the images we get with ^{99m}Tc-teboroxime are significantly superior to those generated by thallium. Despite the sharper images generated, that does not necessarily mean that we can obtain greater diagnostic information from them. The only thing that we can be sure of—as clinical investigations are on-going—is that ^{99m}Tc-teboroxime images are produced in less than two hours, whereas thallium studies may require up to five or six hours. This is a great advantage to patient convenience and patient throughput." Dr. Leppo also adds that "the high resolution of ^{99m}Tc-teboroxime images means that they are ill-suited for use with single-head cameras and are better suited to be used with multi-headed scintillation cameras."

In contrast to ^{99m}Tc-teboroxime, technetium-99m-sestamibi demonstrates very slow myocardial clearance, which

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allows for extended imaging times and results in image quality that is superior to both thallium and ^{99m}Tc-teboroxime, according to Dr. Maddahi. "[The] nearly negligible redistribution and high count rates [of ^{99m}Tc-sestamibi] make gated SPECT imaging possible, and also allow for the assessment of acutely ischemic patients by uncoupling the time of injection from the time of imaging."

Ready availability is an advantage of both agents. According to H. William Strauss, MD, professor of radiology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, availability makes the technetium labeled agents particularly valuable in acute-care settings. "A readily available quick, on-site perfusion agent could allow prompt screening of emergency room patients to determine their coronary status," he says. "Patients with acute myocardial infarction. . .could be imaged before and after thrombolytic therapy to measure the amount of myocardium at risk and determine the degree of salvage following reperfusion. This could help physicians decide who should be considered for mechanical, or surgical, reperfusion of an artery."

According to Robert F. Carretta, MD, assistant clinical professor of radiology, University of California, Davis, director of the department of nuclear medicine, Roseville Hospital, Roseville, California, ^{99m}Tc-teboroxime will also greatly improve patient throughput. He says that ^{99m}Tc-teboroxime "can enhance the productivity of existing equipment and staffs and, in some cases, may enable imaging centers to forego facility expansion and scanner purchases." Dr. Bellinger notes that ^{99m}Tc-teboroxime "offers convenience and scheduling flexibility, especially for a busy laboratory." Dr. Carretta is researching the cost-effectiveness of ^{99m}Tc-teboroxime. According to Dr. Carretta's preliminary investigations, "we can do about two more studies per day with ^{99m}Tc-teboroxime than we can with thallium."

The sensitivity and specificity of ^{99m}Tc-teboroxime have been determined by numerous clinical investigations. In a clinical study of 155 patients, using planar imaging techniques, the results of which were published in the October 1990 issue of *The Journal of the American College of Cardiology,* Dr. Hendel and colleagues reported sensitivity and specificity of 83.2% and 92.1%, respectively, for ^{99m}Tc-teboroxime—data that compare well with thallium results. The average interval between the rest study and the exercise scan was only 97 minutes with ^{99m}Tc-teboroxime, and between 4 and 24 hours with the thallium. Furthermore, the results from ^{99m}Tc-teboroxime imaging agreed with thallium imaging in 90.4% in patients who underwent both procedures, thus indicating a close diagnostic correlation.

As for ^{99m}Tc-sestamibi, clinical trials indicate that it is equal to thallium for the detection of CAD and that it also accurately detects and localizes myocardial infarction and can accurately assess both left and right ventricular ejection fraction by the first-pass technique, according to Maddahi. "Our investigations have revealed that rest-stress studies may be done on the same day with ^{99m}Tc-sestamibi, and that it may be used to assess the results of thrombolytic therapy," he says.

TABLE 1

A Comparison of the Physiologic and Imaging Properties of the Newly FDA-Approved Technetium-99m-Labeled Myocardial Perfusion Agents.

	^{99m}Tc-sestamibi	^{99m}Tc-teboroxime
Peak myocardial extraction fraction	0.65	0.90
Myocardial Clearance (half-time)	5 hours	10-15 minutes
Redistribution	negligible	possible
Myocardial counts	excellent	transiently excellent
After injection imaging begins:	30-60 minutes	1 minute
Time of complete rest/stress study	3-4 hours	0.5-1 hour
SPECT studies	yes	possible
Gated SPECT	yes	no

Future Applications of Technetium-Labeled Agents

"Since the clinical applications of ^{99m}Tc-sestamibi and ^{99m}Tc-teboroxime are at a relatively early stage," says Dr. Hendel, "the clinical protocols to be used with these agents are still evolving. We do not have enough data to definitively assert their prognostic capabilities."

Commenting on the general implications of these new technetium-labeled myocardial imaging tracers in a recent issue of the *American Journal of Cardiology,* Heinz Sochor, MD, department of cardiology, University of Vienna, Austria, wrote, "Further studies. . .will soon enhance our knowledge about.. [these] new tracers, and are likely to give new emphasis and importance to the application of cardiovascular nuclear medicine procedures in general and per-

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fusion imaging in particular."

While ^{99m}Tc-sestamibi and ^{99m}Tc-teboroxime are likely to replace thallium-201 in many cardiac imaging applications, Dr. Wackers maintains that "thallium will not vanish from cardiac studies. Indeed, it is especially effective in the assessment of myocardial viability, so I think this tracer will remain a fixture in nuclear cardiology laboratories."

I.V. Persantine

The Du Pont Merck Pharmaceutical Co. has also received approval from the FDA to market I.V. Persantine® (dipyridamole USP), the first pharmacologic alternative to exercise thallium stress testing for the evaluation of CAD in patients who cannot adequately exercise.

"This patient population would include people suffering from peripheral vascular diseases, orthopedic problems, severe lung disease, neurological diseases, musculoskeletal diseases, arthritic disorders, amputees, patients with beta blockers, and those who are markedly obese," says Lewis C. Becker, MD, professor of medicine, Johns Hopkins Medical Center, Department of Cardiology, Baltimore, Maryland. "Essentially, Persantine will afford us the ability to diagnose more people, identify those who are at a high risk for contracting CAD, and select people for cardiac catheterization."

"The clinical protocol for the study includes intravenous infusion of I.V. Persantine over 4 minutes, thallium injection, and image collection within minutes," says Dr. Leppo. "A second set of images, without any additional injection, is collected three to four hours later. Both sets of images are compared to differentiate ischemic tissue from infarcted tissue."

According to clinical investigators, the study results derived from I.V. Persantine are equivalent to those of maximal exercise testing with thallium and are superior to the results for patients who cannot complete the exercise tests. "The procedure will provide clinical information that until now had been unavailable in these patients without invasive testing," adds Dr. Leppo.

"Adequate stress levels are needed to identify optimal myocardial perfusion with thallium," explains Charles A. Boucher, MD, associate physician in cardiology, Massachusetts General Hospital, associate professor of medicine, Harvard Medical School, Boston, Massachusetts. "[But] some patients with orthopedic limitations, peripheral vascular disease, lung disease or other medical condition, cannot exercise to peak levels." I.V. Persantine simulates the effects of exercise pharmacologically during thallium studies by increasing blood flow to the heart and allows evaluation of myocardial perfusion. This represents a significant advance in cardiac imaging, expanding the diagnostic capabilities of the cardiologist."

There exist, however, a few drawbacks to the use of I.V. Persantine. "The test should be used with caution in patients with unstable angina, severe asthma, or bronchospasm," warns Dr. Boucher. Furthermore, while both the exercise-thallium test and the I.V. Persantine-thallium test allow the physicians to assess the ability of the coronary arteries to deliver blood to the heart muscle, the exercise test still provides a better measure of the hearts reaction to the high oxygen demand and other systemic effects of exercise which are absent with the I.V. Persantine/thallium test.

Investigators have also reported mild adverse effects with I.V. Persantine, including dizziness, headaches, and nausea—although these adverse effects can usually be reversed within minutes after the administration of intravenous aminophylline. "About 1 in 1,000 patients administered with Persantine develop myocardial ischemia," says Robert J. Boudreau, MD, director, division of nuclear medicine, University of Minnesota, Minneapolis, Minnesota. "This compares to 3 in 10,000 for people who undergo treadmill testing"

While the oral form of Persantine became available in the 1950s in Europe for relief of angina pectoris, development of the intravenous form of the drug did not get underway until the 1970s by Boehringer Ingelheim International GMBH, of Ingelheim Am Rhein, Germany. It has been tested clinically at 116 sites worldwide since 1978, and was approved for routine use in the United Kingdom in 1987.

Du Pont Merck received an exclusive license to market I.V. Persantine in the U.S., and the company projects that 20%–30% of all thallium studies will use I.V. Persantine. According to Du Pont Merck, more than 1.5 million thallium studies were performed last year in the U.S., and the company anticipates a continued growth rate of 20% per year for the next five years.

While I.V. Persantine is currently approved for use only in conjunction with thallium studies, "Ongoing research with I.V. Persantine, " says Kenneth Brown, MD, University of Vermont College of Medicine, cardiology unit, Burlington, Vermont, "indicates it may have a prognostic utility for assessing cardiac risk in preoperative vascular surgery and post-myocardial infarction patients."

Pharmacologic stress testing with intravenous Persantine may also be used in conjunction with ^{99m}Tc-teboroxime and ^{99m}Tc-sestamibi, "potentially shortening the pharmacologic stress studies," wrote Lynne Johnson, MD, in a recent issue of *The American Journal of Cardiology.* "The very different pharmacokinetics of the [two] technetium perfusion imaging agents present a definite choice to nuclear imaging laboratories," she added.

The FDA's approval of the two new technetium-labeled agents and the intravenous form of Persantine opens the door on a new class of tracers for imaging the heart, thus advancing the evolution of nuclear cardiology. "It signifies to me," says Dr. Moore, "that the radiopharmaceutical industry has committed itself to advancing myocardial perfusion. I also hope that this leads to the development of more metabolic tracers."

Palash R. Ghosh