Recent Advances in Radiopharmaceuticals

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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) give an overview of the new radiopharmaceuticals developed over the last five years, (2) list and compare the new radiotracers used to image the heart and the brain, and (3) identify the newer agents being utilized for therapy.

Over the last two years, several new diagnostic radiopharmaceuticals have been approved. Three are for myocardial imaging (teboroxime, sestamibi, and the rubidium-82 generator, in addition to the pharmacologic stress agent dipyridamole USP); one is for cerebral perfusion imaging (exametazime); and one is for renal imaging (mertiatide). In addition, there are new, exciting therapeutic agents for palliation of bone pain. These recently approved radiopharmaceuticals demonstrate the growing importance of nuclear medicine to the health of mankind.

INTRODUCTION

One of the success stories of the peaceful use of the atom is the discovery and development of technetium-99m (^{99m}Tc) radiopharmaceuticals for use as noninvasive diagnostic agents. The element technetium was identified by Perrier and Segre in 1937 (*1*). Two years later, ^{99m}Tc was discovered (*2*). Only a few years after that, the molybdenum-technetium pair was separated in the midst of analyzing fission products at Brookhaven National Laboratory (*3*). This new radioisotope, eluted from a molybdenum generator in the form of pertechnetate, was soon tested as a diagnostic agent (*4*). At present, more than 85% of the diagnostic procedures carried out in nuclear medicine use ^{99m}Tc radiopharmaceuticals (*5*).

Two important advances led to the rapid proliferation of ^{99m}Tc in nuclear medicine: the further development of a generator that could be eluted with isotonic saline (*6*) and the development of a single-vial kit containing both stannous ion (as the reducing agent) and the chelating agent (*7*). These so called "instant kits" produce a high yield radiopharmaceutical in one step upon the addition of pertechnetate. Many of the early compounds were chosen to trace the function of the blood-purifying organs, i.e., the lung, the liver, and the kidney. However, these functional studies were often confused with efforts to obtain anatomical detail. In cases in which anatomical changes occurred at the same rate as functional changes, the higher resolution techniques of computerized tomography (CT) and, more recently, magnetic resonance imaging (MRI) became the diagnostic modalities of choice. For example, nuclear medicine procedures that were mainly anatomical, such as brain imaging to detect a disrupted blood-brain barrier, have become less important.

There are cases, however, in which function changes more quickly than anatomy, e.g., in bone metastases. Here, nuclear medicine remains an important adjunct to diagnosis. Likewise, measurement of myocardial perfusion with thallium-201 (^{201}Tl) or the new ^{99m}Tc agents also provides early and important information. Certainly, the established agents such as ^{99m}Tc-DTPA (diethylenetriaminepentaacetic acid), ^{99m}Tc sulfur colloid, ^{99m}Tc-MAA (macroaggregated albumin), ^{99m}Tc-DADS [N,N']bis(mercaptoacetamido)-ethylenediamine], and the ^{99m}Tc bone agents distribute proportionally to flow, and if they are used to measure physiologic changes, they are also important diagnostic tools. It is clear from these examples that nuclear medicine must concentrate on the measurement of small vessel perfusion and not anatomy.

COMPLEMENTARY DIAGNOSTIC MODALITIES

Iodinated contrast agents used in CT have not progressed beyond polar compounds that distribute in the extracellular space and then are filtered by the glomeruli. Contrast agents for MRI are presently at the same stage of development, e.g., gadolinium (Gd) labeled DTPA is an agent comparable to ^{99m}Tc-DTPA in its biodistribution. Agents comparable to the nuclear medicine agents used for hepatobiliary studies are also being tested. Iron oxide colloids that will measure phagocytic function and thus mirror the studies being done with ^{99m}Tc sulfur colloid are also under investigation. Because of the lesser requirements for the amount of contrast agent per kilogram of body weight for MRI compared to CT, it may be possible to study small vessel perfusion and selected biochemical reactions using proton MRI with paramagnetic contrast agents. But nuclear medicine has the clear advantage because of the "carrier free" nature of radiopharmaceuticals.

Besides being used for perfusion measurements, radiopharmaceuticals can also be applied to the measurement of biochemical reactions (*8*). On the other hand, attempts to use

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TABLE 1. Nomenclature

Trade Name	Generic Name	Abbreviation
CardioTec	Teboroxime	SQ 30217. MeB-CDO
Cardiolite	Sestamibi	RP-30, MIBI
Technescan MAG_3	Mertiatide	MAG_3
Ceretec	Exametazime	HMPAO
I.V. Persantine (for ^{201}Tl)	Dipyridamole, USP	
Cardiogen-82	Rubidium-82 Generator	

iodinated contrast media with CT to measure perfusion have not been successful (*9*). Iodinated contrast media have not been used in the diagnosis of biochemical changes since their development in the 1920s because of the large concentration of iodinated compound required to affect the image (*10*). As noted, magnetic resonance contrast media that change the relaxation times of the proton are now being developed to better define anatomical changes and functional changes in major organ systems by analogy with the early nuclear medicine studies (*11*).

RECENTLY APPROVED RADIOPHARMACEUTICALS

There are many exciting advances in the measure of perfusion and biochemistry using radiopharmaceuticals. Most of this excitement comes from the general availability of a number of new radiopharmaceuticals recently approved by the Food and Drug Administration (FDA) (Table 1). Both single-photon emitting (SPE) and positron emitting (PE) radiotracers are available for measuring perfusion in the heart and the brain with a normal blood-brain barrier. The increased sensitivity of PET allows for the use of both diffusible and microsphere analogs, whereas SPE radiotracers have mostly been based on microsphere analogs. The recent introduction of more sensitive multihead/ring SPECT (*12*) has optimized the use of SPE diffusible tracers, especially in the heart, e.g., ^{99m}Tc-teboroxime (*13*). Perfusion can now be adequately measured with SPE radiotracers to the sensitivity required in most clinical situations.

The strontium-82/rubidium-82 ($^{82}SR/^{82}Rb$) generator has allowed myocardial perfusion to be measured with PET without the expense of a cyclotron (*14*). Rapid repeat studies are possible with ^{82}Rb because of its 75-sec physical half-life. Although not approved by the FDA, ^{18}F-2-fluoro-2-deoxy glucose (FDG) and ^{15}O-H_2O have been used extensively in research studies. The measure of tumor aggressiveness (*15*) and focal epilepsy (*16*) are two areas of clinical application for FDG. There are many exciting advances in the measure of perfusion and biochemistry using radiopharmaceuticals.

Table 1 contains the trade names, generic names, and various abbreviations for the recently FDA-approved radiopharmaceuticals. The chemical structures are given in Figure 1. The preparation conditions for these new radiopharmaceuticals are given in Table 2. In general, the preparation is more complicated than that needed for the previously established kits, but still falls under the general concept of "instant" kits.

Two major target tissues, the myocardial muscle and the cerebrum with a normal blood-brain barrier, can now be studied with ^{99m}Tc-labeled compounds. In the heart, ^{201}Tl, as the thallous cation, is most often used. However, ^{99m}Tc cations are being tested to determine their suitability as myocardial perfusion agents. These cations include hexakis (2-methoxy-2-methylpropyl isonitrile), also known as sestamibi (*17*) and RP-30, and neutral ^{99m}Tc complexes such as [bis]1,2-cyclohexanedionedioximato(1')-O]-1,2-cyclohexane-dione-dioximato(2-cyclohexane-dione-dioximato(2)-O]methylborato(2)-N,N',-N'',N''',N''''N''''']-chlorotechnetium, which is one of a class of boron adducts of technetium dioximes (BATOs), also known as teboroxime, CardioTec, SQ 30,217, or CDO-MeB (*18–20*).

Although these two radiopharmaceuticals are both indicated for use as myocardial perfusion agents, their biological properties are vastly different. Sestamibi is a positively charged, lipid soluble, ^{99m}Tc complex that appears to be bound in the mitochondria of myocytes by virtue of the transmembrane potential (*21*). Sestamibi is taken up by the myocardium and retained with a half-life of greater than 12 hr, whereas ^{99m}Tc-labeled teboroxime is taken up rapidly and released rapidly (*22*). With teboroxime, the imaging must be completed within the first ten min after injection. The latter

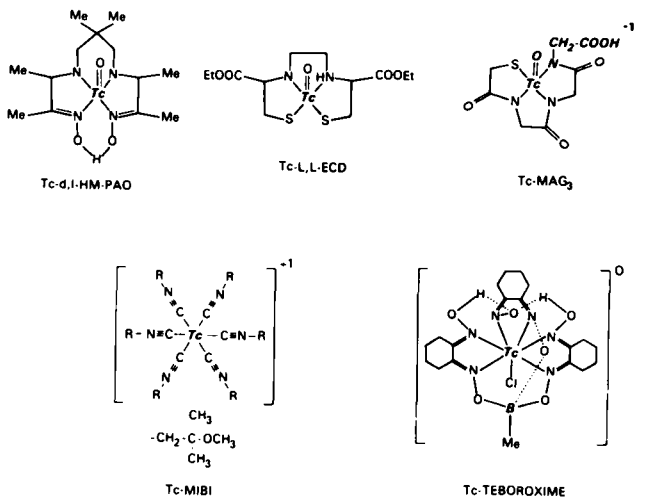


FIG. 1. Structure of Tc-d,l-HMPAO (exametazime), Tc-L,L-ECD, Tc-MAG_3 (mertiatide), Tc-MIBI (sestamibi), and Tc teboroxime (teboroxime).

TABLE 2. Preparation Conditions

Radiopharmaceutical	Protocol for Preparation
CardioTec	Heat for 15 min at 100°C
Cardiolite	Heat for 10 min at 100°C
Ceretec	Generator within 24 hr; Use within 30 min
MAG_3	Add 2 ml of air; Heat for 10 min at 100°C
Cardiogen	Use with Infusion System

compound is more characteristic of xenon than of thallium and can be used to obtain rapid repeat studies. Teboroxime is a neutral compound that is more highly extracted than thallium and significantly higher than sestamibi and should, therefore, be more sensitive to small changes in flow, especially during a stress test. Neither of the ^{99m}Tc-labeled radiopharmaceuticals "redistributes" to the extent that ^{201}thallium does. Therefore, two injections are required to obtain a stress and a rest study. There have been recent efforts to view the net efflux of teboroxime from the heart as "redistribution" (*23,24*).

A recent review of cardiac imaging with sestamibi and teboroxime by Leppo, DePuey, and Johnson, which culminates a series of ten articles on these two heart agents, appears in the October 1991 edition of *The Journal of Nuclear Medicine* (*25*). Both heart agents were approved at the end of 1990 and their use is rapidly expanding the type of information obtained in diagnostic myocardial perfusion studies.

Xenon-133 (^{133}Xe) is approved by the FDA for the measurement of cerebral perfusion. Iodine-123 (^{123}I) labeled N-isopropylamphetamine (*26*) (SPECTamine) became the second commercially available agent that crosses the intact blood-brain barrier, in 1989. The distribution immediately after injection is flow related, but the immediate uptake and later distribution are dependent on amine uptake processes.

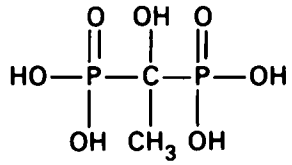
Recently, a number of neutral ^{99m}Tc-labeled compounds were proposed for measuring cerebral blood flow in disease states in which the blood-brain barrier is intact. The series of propyleneamineoximes (PNAOs) are interesting cerebral perfusion agents (*27*). Whereas ^{99m}Tc-PNAO is taken up efficiently and released from the cerebrum rapidly, a derivative, ^{99m}Tc, d,l hexamethylpropylene-amine oxime (HMPAO, exametazime) is taken up and retained. The mechanism of retention is thought to be binding to glutathione in the brain, although this is far from proven (*28*). The available rotating SPECT instrumentation is relatively insensitive, so HMPAO has been studied in the clinic since its approval by the FDA in 1989. However, with the proliferation of multihead SPECT machines, those compounds with fast pharmacokinetics may be more useful since repeat studies can be carried out with minimal delay. The analogy with myocardial imaging agents is important.

Finally, there is an ester derivative of the diamino, disulfide chelation system (N,N'-1,2 ethylenediyl-bis-L-cysteine diethylester, Bicisate, Neurolite and Tc-ECD) that is taken up in the human brain (*29*). This compound depends on the slow hydrolysis of the ester groups in the blood and the rapid hydrolysis of ester groups in the brain to give high cerebral uptake and retention of the more hydrophilic metabolite. It appears that a series of first generation ^{99m}Tc compounds have been developed to measure perfusion in the brain; these hold great promise for establishing the usefulness of nuclear medicine studies of cerebral perfusion in diseases that do not disrupt the blood-brain barrier. Dementia and stroke are the two most frequently mentioned abnormalities.

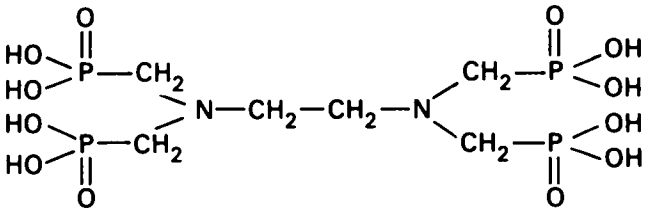
NEW THERAPEUTIC AGENTS

In addition to the recent advances in diagnostic radiopharmaceuticals, there have been a number of new therapeutic radiopharmaceuticals approaching clinical reality. Recently, Volkert et al. reviewed the available therapeutic radionuclides (*30*). Therapy has always been a major part of nuclear medicine, and the new series of radiopharmaceuticals being developed promises to expand the field considerably. While the community awaits a number of diagnostic monoclonal antibodies to be approved and then extended to therapy, the next class of compounds closest to routine clinical use are the agents designed to treat bone pain from skeletal metastases. These are strontium-89 (^{89}Sr) chloride, now approved in Canada, rhenium-186 hydroxyethylidene diphosphonate (^{186}Re-HEDP), and samarium-153 ethylenediaminetetramethylene phosphonic acid (^{153}Sm-EDTMP). The chemical structures for HEDP and EDTMP are given in Figure 2.

Important considerations for these therapeutic agents are the energy of the beta particle and the physical and biological half-life. The beta energy should be such that adjacent cells are destroyed, but should not be high enough to cause radiation damage to the sensitive bone marrow. The biological half-life should be such that the radiopharmaceutical localizes quickly in the bone, but clears the rest of the body rapidly.



HEDP



EDTMP

FIG. 2. Structure of HEDP (hydroxyethylene diphosphonate) and EDTMP (ethylenediaminetetramethylene phosphonic acid).

The shortest physical half-life that is consistent with the biological half-life will deliver the maximal dose rate to the bone. Also of interest are the beta emitting colloids for radiation synovectomy and the radiolabeled particles for intraarterial treatment of tumors.

Over the last five years there has been an encouraging increase in the number of new radiopharmaceuticals for the diagnosis of physiologic changes in the heart, brain, and kidney, as well as for therapy in bone metastases, arthritis, and liver cancer.

CONCLUSION

These advancements bode well for the continuing usefulness of nuclear medicine in the diagnosis and therapeutic treatment of disease. The success of these radiopharmaceuticals and further developments in the field is possible only if these radiopharmaceuticals take maximal advantage of the uniqueness of the tracer principle, i.e., they are designed to give optimal information on changes in flow and biochemistry. With the recent improved imaging resolution and the unique ability to trace changes in perfusion and biochemical processes by external imaging, radiopharmaceuticals are capable of providing anatomically distinct, physiologic information by noninvasive means.

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