Radiopharmaceuticals for Brain Imaging: The Technologist's Perspective

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This is the fourth article in a six-part series on new radiopharmaceuticals. Upon completion of this article, the nuclear medicine technologist will be able to describe the evolution of SPECT neuroimaging and discuss the current brain perfusion radiopharmaceutical characteristics.

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The purpose of this article is to describe the characteristics of brain perfusion radiopharmaceuticals designed for use with single-photon emission computed tomography (SPECT) systems. Attention is given to preparation, injection parameters, and quality control issues for each agent. Specific procedures for kit preparation and quality control methods for the pharmaceuticals are presented.

The most significant differences between tracers are in the preparation and stability of the dose, as well as injection parameters. These issues are discussed in terms of the technologist's role in performing brain imaging studies. This will grow as new agents, in particular, those used to study brain receptors become more generally available. As brain perfusion imaging continues to advance, there will be new and exciting challenges for the nuclear medicine technologist.

EVOLUTION OF BRAIN SPECT

Cerebral perfusion imaging with SPECT is a rapidly evolving area in nuclear medicine. SPECT imaging of the brain using inhaled xenon-133 (^{133}Xe) has been available for some time. The introduction of iodine-123 (^{123}I) labeled amines to image regional cerebral blood flow (rCBF), in combination with rotating gamma cameras, has reawakened interest in cerebral perfusion imaging by the nuclear medicine community.

Brain perfusion agents designed for use in combination with SPECT systems became generally available to nuclear medicine laboratories for clinical studies in 1988. Thus, rCBF/SPECT studies for the evaluation of central nervous system (brain) disorders are now routinely performed in many nuclear medicine laboratories. However, new applications for SPECT neuroimaging are still evolving.

Two factors account for the continuing evolution of SPECT neuroimaging; one is related to the development of multidetector and dedicated imaging systems, which are well suited for brain studies. The other is the commercial availability of radiopharmaceuticals for clinical brain imaging, such as [^{123}I]iodoamphetamine (IMP) and technetium-99m (^{99m}Tc) hexamethyl propylene amine oxime (HMPAO). In addition, new agents are being developed. One, ^{99m}Tc-bicisate, more commonly known as ^{99m}Tc-ECD, has been submitted to the Food and Drug Administration (FDA) for regulatory approval.

Another important advance for SPECT neuroimaging is the development of a class of agents for the study of specific brain receptors, e.g., dopamine and opiate. Receptor agents are being evaluated in Europe, Japan, and the United States. Because these receptor agents are not generally available to laboratories, a discussion of their properties and applications is beyond the scope of this report.

This paper focuses on the commercially available SPECT brain perfusion imaging radiopharmaceuticals. Although ^{99m}Tc-ECD is not yet commercially available, Phase III studies on the agent have been completed. It is anticipated that ^{99m}Tc-ECD will enter the marketplace in the relatively near future. Therefore, we believe it is appropriate that the brain perfusion imaging characteristics of this agent be discussed.

These agents will be examined in terms of dosage, preparation, quality control, and general imaging parameters as they impact on the nuclear medicine technologist. In addition, some of the current clinical applications using these agents are reviewed.

[^{123}I]IMP

The agent [^{123}I]IMP (SPECTamine, IMP Inc., Schaumburg, IL) was the first radiopharmaceutical to receive FDA approval for brain perfusion imaging. The initial indication was for evaluating rCBF in cerebrovascular disease (stroke). However, research has demonstrated the utility of using this

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and other brain perfusion agents for evaluating dementia (including Alzheimer's disease), transient ischemic attacks (TIAs), head trauma, and epilepsy. In addition, there is promising work being done with this agent and other agents for their use in the study of psychiatric disease.

IMP is a lipophilic amine that is labeled with ^{123}I, which, with its half-life of 13.2 hr and energy of 159 keV, is a good tracer for imaging with a gamma camera. This agent is provided in a unit dose, with no radiochemical purity testing needed on-site. The recommended dose is 3-6 mCi (111-222 MBq) (*1*).

Because IMP is lipophilic, it crosses the blood-brain barrier. (Historically, nuclear medicine could image only areas where the blood-brain barrier had been disrupted due to stroke, tumor, or trauma.) IMP localizes in the gray matter of the brain in proportion to rCBF, allowing for distinction between gray and white matter, binding to nonspecific amine receptors. IMP images provide information relative to perfusion to the cerebral cortex and deep brain structures, e.g., basal ganglia.

Uptake of IMP occurs in the brain immediately after injection and sharply increases over a short period. Peak activity occurs ~20 min postinjection. The tracer maintains a "steady state" in the brain for ~45-50 min following peak uptake. This provides a window for SPECT imaging. The "steady state" is a function of tracer accumulating in the brain at the same rate as it washes out. Wash-in of IMP is facilitated by a large accumulation of tracer in the lungs, which is continually released into blood plasma. Over the first hour following injection, the distribution of IMP in the gray matter can change between 5% and 10%. Therefore, IMP images obtained 1 hr or more postinjection begin to reflect a loss of gray and white matter distinction.

Some clinicians claim that the dynamic redistribution of IMP in gray matter reflects reperfusion. Delayed images can be obtained in a manner similar to that used in thallium-201 (^{201}Tl) imaging of cardiovascular disease. Comparison of 20-min postinjection and 3-hr delayed images have been hypothesized to have prognostic significance in stroke (*2*). There is no widely accepted description of the mechanism that explains the redistribution. The clinical significance of redistribution as a prognostic indicator for stroke recovery remains controversial.

Patient preparation prior to IMP injection is simple. Two or three drops of Lugol's solution (in orange juice) is given 30 min before injection. This iodinated solution functions as a block for any free ^{123}I uptake in the thyroid.

Injection technique for IMP varies among laboratories. At the Medical College of Wisconsin, technologists position the patient on the imaging table before inserting a butterfly needle and stopcock with a saline flush. This may minimize a reaction to pain and anxiety associated with the needle stick before the tracer is injected. The patient remains still during the uptake of IMP, a period of ~15 min. During this interval, a final check on camera rotation and patient positioning can be made.

^{99m}Tc-HMPAO

Technetium-99m-labeled agents are ideally suited for rCBF/SPECT imaging. PnAO was introduced as an experimental blood flow tracer by Volkert et al. in 1984 (*3*) and was the precursor to ^{99m}Tc-HMPAO (Ceretec, Medi-Physics, an Amersham Co., Arlington Heights, IL) described by Holmes et al. (*4*). Since its introduction, HMPAO has gained general acceptance in the nuclear medicine community and is now an FDA-approved commercially available product. It is available in kit form and requires preparation by the nuclear medicine technologist.

HMPAO is similar to IMP, in that it is a lipophilic substance, which can cross the blood-brain barrier. It converts rapidly from the lipophilic to the hydrophilic state and thus becomes trapped in gray matter. This conversion process occurs in vitro as well, so it is necessary to maintain a close relationship between time of kit preparation and injection. Once trapped in the brain, HMPAO remains stable with little wash-in or wash-out effect over 6-8 hr (*5*). Unlike IMP, the retention of HMPAO is not dependent on the presence of receptors. "Luxury perfusion" (where rCBF exceeds metabolic needs) is ordinarily more apparent with HMPAO than IMP. This is presumably due to the lack of receptors for IMP retention.

For reconstitution of HMPAO, the package insert recommends using fresh eluate (≤ 2-hr old) from a molybdenum-99 (^{99}Mo)/^{99m}Tc generator that has been eluted within 24 hr. This is necessary because there is a very low concentration of stannous ion in the kit and poor quality pertechnetate (an increased ^{99}Tc/^{99m}Tc ratio) can adversely affect labeling efficiency (*4*). We have had good results with older pertechnetate, e.g., Monday morning elutions. However, because our generators are eluted 5-7 times per week, there are few instances when elution has occurred >24 hr previously. The package insert also recommends an upper limit of 30 mCi of pertechnetate for reconstitution of a vial.

The recommended interval between reconstitution and injection of HMPAO in the package insert is stated as less than 30 min. However, we have found that waiting longer than 15 min significantly degrades the quality of the preparation. In fact, we make an attempt to inject within 5 min postreconstitution. As the amount of radiolabeled lipophilic component decreases over time following the addition of pertechnetate, there is a corresponding increase in background activity, which will appear in the images. The presence of this activity can reduce image quality and thus interfere with image interpretation. To further allow clearance of potential residual background activity, we recommend initiating image acquisition at 1.5–2 hr postinjection. Borys has indicated that a stable formulation of HMPAO has been developed (N. Borys 1992, personal communication). However, the stable formulation is not yet commercially available.

The basic reconstitution procedure for HMPAO is straightforward, essentially a "shake and bake" operation. Radiochemical purity testing, as recommended in the package insert, is more complex. The package insert describes a

three strip/three solvent method, which identifies the lipophilic component, free pertechnetate, and reduced-hydrolyzed ^{99m}Tc. However, the essential information needed by the technologist is the percent of the lipophilic component. This can be determined using a single strip/single solvent method as initially described by Hung et al. (*7,8*). This ether extraction method uses ethyl acetate and Gelman solvent saturation pads or Whatman paper.

The procedure at the Medical College of Wisconsin is to use 3″ × 5″ mini-strips cut from Gelman pads. The strip is spotted with ^{99m}Tc-HMPAO, 0.5 in. from the bottom, placed in the ethyl acetate, and the lipophilic component is allowed to migrate toward the top of the strip for ~1 min. The strip is then cut in half and each of the halves is counted in either a well counter or a dose calibrator. If a dose calibrator is used, then it is essential to use a very large drop and to subtract background counts.

Results obtained with the single strip method correlate well with those obtained using the method described in the package insert. Using this single strip method, we are able to inject patients within 5 to 10 min after reconstitution. This enables us to inject a dose at the patient's beside within 15 min of reconstitution, if necessary, e.g., ictus or immediate postictus injections in epilepsy patients. Using this procedure, the quality control procedures can be completed prior to injecting the patient.

Although HMPAO is sold as a single-dose vial, we have had good results with preparing two injections from one vial. (Medi-Physics, the manufacturer of HMPAO, states that it is not meant for multiple doses. The company does not recommend such usage of the product [N. Borys 1992, personal communication].) To do this, it is necessary to have the patients available and ready for injection. The procedure requires that 75mCi of pertechnetate be added to the HMPAO vial, quality control (one strip method) be performed, and then two doses withdrawn and immediately injected. This can become a logistical problem, trying to schedule patients and find an area large enough to inject two patients simultaneously. We have found it helpful to have butterfly needles and stopcocks already in place before the kit is reconstituted. Scanning is then scheduled at 45-min intervals, beginning 1.5 hr after the injection.

Piera et al. (*9*) reported success in splitting the HMPAO vial into as many as five doses. This was done by reconstituting the vial with 5 ml of normal saline and separating the volume into five 1-ml aliquots. These aliquots were refrigerated for up to 4 hr and labeled with pertechnetate immediately prior to injection. Radiochemical purity was assessed for the refrigerated aliquots at up to 4 hr. Piera reported a mean percent lipophilic component of 94% ± 2.0% in the HMPAO that had been refrigerated for 4 hr. We have not found this technique to be reliable in our laboratory.

The use of potassium perchlorate (300 mg in orange juice) when injecting HMPAO has been suggested. This chemical, given orally 30 min before HMPAO injection, would block the thyroid and choroid plexus from any free pertechnetate (*10*). Our experience at the Medical College of Wisconsin is that by injecting within 10 min of kit reconstitution, the level of free pertechnetate is minimal, and no potassium perchlorate is necessary.

The injection technique for HMPAO is important. Using a stopcock and butterfly needle with a saline flush, 10-30 mCi (370-1110 MBq) of HMPAO is injected. HMPAO should not be mixed with blood in the syringe (*10*). Using a butterfly needle, the technologist can find a vein and have the patient prepared before reconstitution of the vial.

Environmental stimuli (such as noise and light) are important factors in establishing which room to use for injection of HMPAO. Studies have shown that uptake of HMPAO in normal brains can be affected by sensory input (*11*). Therefore, the room in which HMPAO is injected should have low ambient light and noise, and the patient should not talk, be spoken to, or moved during the 8-10-min pre- and postinjection period. It is helpful to explain this to the patient: tell the patient that after the tracer is injected, he or she should sit still and not talk for 10 min. Both light and room noise should be kept as constant as possible.

^{99m}Tc-Bicisate

This agent, commonly known as ^{99m}Tc-ECD (Neurolite, Du Pont Merck Pharmaceutical Company, N. Billerica, MA), is another ^{99m}Tc-based radiopharmaceutical developed for rCBF imaging, which has been submitted to the FDA for regulatory approval. Clinical trials with this agent in normal subjects and stroke patients indicate that SPECT images will provide information similar to that obtained with currently available tracers (*12*).

When it becomes available, Neurolite will be in a two-vial kit form for labeling with sodium [^{99m}Tc]pertechnetate to produce ^{99m}Tc-bicisate. To reconstitute the kit, 100 mCi of [^{99m}Tc]pertechnetate, in ~2.0 ml, is added to the buffer vial. With another syringe, 3.0 ml of sodium chloride is rapidly added to the lyophilized contents in the buffer vial. The contents of the vial are shaken for a few seconds, then allowed to stand for 30 min at room temperature. Radiochemical purity testing is performed using a single solvent/single strip thin layer chromatography procedure (*13*). This radiopharmaceutical is stable in vitro.

In the clinical trials, a single dose of ^{99m}Tc-bicisate was obtained from each kit and injected within 2 hr of reconstitution. This kit is intended as a single-use preparation. Peak brain uptake of ^{99m}Tc-bicisate occurs within 5-min postinjection and slowly drops over several hours. The administration technique for ^{99m}Tc-bicisate is similar to that for HMPAO; during the immediate pre- and postinjection period, noise and light stimuli should be kept to a minimum. Optimum SPECT brain images are acquired at 2-hr postinjection of ^{99m}Tc-bicisate, although imaging can be initiated 20 min after injection without significant background artifacts.

DISCUSSION

At the time this paper is being prepared, the only commercially available rCBF tracer is HMPAO. We anticipate

that IMP will again become available and ^{99m}Tc-bicisate is currently under review by the FDA.

Differences in method of localization, amount of uptake, rate of uptake, and wash-out among the three tracers are documented. These differences contribute to variations in the appearance of rCBF/SPECT images in abnormal subjects. Most of these variations relate to gray and white matter distinctions and acute changes in cortical perfusion. Research is being conducted to determine which of these agents is most appropriate for the evaluation of specific disease states such as dementia, cerebrovascular disease, and psychiatric disorders.

From the technologist's standpoint, the most notable differences among these tracers are in the preparation and stability of the dose and injection parameters. IMP, when available, requires the least technologist preparation time. However, because it comes from a commercial radiopharmacy in a unit dose, delivery times and availability may vary geographically. Depending on location, doses may need to be ordered one day in advance; this limits the use of this tracer in acute or on-call situations. Imaging must be performed 15-20 min postinjection, which limits flexibility in patient scheduling. Redistribution images may be acquired, which may contribute to the patient's prognosis in cerebrovascular disease.

HMPAO comes in a kit form, and thus can be available at all times. Images with ^{99m}Tc have the advantages of higher count rates, the opportunity to use higher patient doses, and optional use of a high resolution collimator. In vitro instability of the reconstituted kit, however, is a disadvantage for the technologist. Patients must be injected within 15 min of reconstitution; injection beyond this time results in greater background activity and less than optimal image quality. While scanning at 1.5–2-hr postinjection is recommended, in emergency situations, images of adequate diagnostic quality can be obtained 10-min postinjection.

HMPAO is sold as a unit dose; however, some laboratories have successfully derived methods for obtaining several doses from a single vial. Stabilized multi-dose vials are likely to be made available from the manufacturer in the future.

The development of radiopharmaceuticals for brain perfusion imaging as described in this report, along with the introduction of new imaging instruments, will increase the demand for brain imaging studies by nuclear medicine. These advances and those yet to come will create an exciting and challenging opportunity for the nuclear medicine technologist.

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