Comparison of IMP and HMPAO for SPECT Brain Imaging

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This is the second article in the four-part series on nuclear medicine updates. Upon completion of this article the reader should be able to compare the (1) technical, and (2) clinical aspects of iodine-123-IMP and technetium-99m-HMPAO for brain perfusion imaging.

Single-photon emission computed tomography (SPECT) functional brain imaging has recently become a standard procedure in most nuclear medicine departments. The Food and Drug Administration has thus far approved two agents—iodine-123-N-isopropyl-*p*-iodoamphetamine ([^{123}I]IMP) and technetium-99m d,l hexamethylpropyleneamine oxime (^{99m}Tc-HMPAO), which can be used with SPECT techniques to image brain perfusion and, indirectly, cerebral metabolism. Although brain imaging results from these two radiopharmaceuticals are often similar, there are a number of important differences to consider when using these agents.

To better understand neurologic disorders, it is essential that the clinician be able to identify alterations in regional brain physiology. Developments within the past decade in nuclear medicine have contributed substantially to our ability to assess physiologic changes which occur in the brain in a variety of central nervous system (CNS) diseases. These developments have come about through the identification of a number of highly lipophilic radiopharmaceuticals which can readily enter the brain and distribute in accordance with some known neurophysiologic processes. The two agents which have received the greatest degree of attention (and which are currently the only two agents available for routine clinical use) are [^{123}I]IMP and ^{99m}Tc-HMPAO. The purpose of this article is to provide the reader with an overview and a comparison of these two neuroimaging agents from both a technical and clinical standpoint.

PHYSIOLOGY AND BIOCHEMISTRY

IMP is related closely in molecular structure to amphetamine. It is a highly lipophilic agent and, as such, readily crosses an intact blood-brain barrier (BBB). This property allows for a very high cerebral extraction fraction (90%) during first-pass transit through the brain. Consequently, the initial distribution of this radiopharmaceutical is directly related to regional cerebral perfusion over a wide range of blood flow values (*1*). Once within the brain tissue the mechanism of retention is based on binding nonspecifically to a variety of amine receptor sites in viable brain synaptosomes (*2*). Peak IMP brain activity (6%–7% of administered dose) is reached ~20 min after intravenous injection (*3,4*). This delay in peak uptake is related, in part, to rapid initial uptake of IMP by lung tissue which then acts as a reservoir for IMP release subsequent to injection (*4*). Within the brain, IMP concentration remains reasonably unchanged between 20 min and 1 hr postinjection. Thereafter, a process often referred to as redistribution takes place resulting in a shift in IMP concentration away from brain gray matter toward the white matter (*5*). The process of redistribution changes the IMP cerebral distribution in such a way that the dependence on blood flow is lost and the distribution is determined primarily by the presence of metabolically viable amine receptor sites (*2,6*). In the presence of an intact BBB the redistribution phenomenon is thought to occur as a result of both wash-in and binding of IMP from other sites in the body (lungs in particular) and regional brain wash-out of IMP metabolites (*7,8*).

Structurally, HMPAO is very dissimilar to IMP (Fig. 1). However, like IMP, HMPAO is extremely lipophilic and readily crosses an intact BBB to distribute in the brain in direct proportion to regional cerebral perfusion (*9*). HMPAO has a slightly smaller first-pass extraction fraction than IMP, but reaches maximum brain uptake (4% of injected dose) in ~3 min (*10*). Unlike IMP, the brain distribution of HMPAO remains essentially unchanged for many hours postinjection (*10*). The mechanism of brain tissue retention of HMPAO is probably the result of reaction with glutathione to form a hydrophilic complex which is unable to move back across the BBB (*11*). Clearance of HMPAO from the blood is somewhat slower than for IMP and within the first hour postinjection there may be significant HMPAO blood-pool activity remaining (*12*). This is the reason some have recommended that image acquisition be delayed for 1–2 hr postinjection of HMPAO (*12*).

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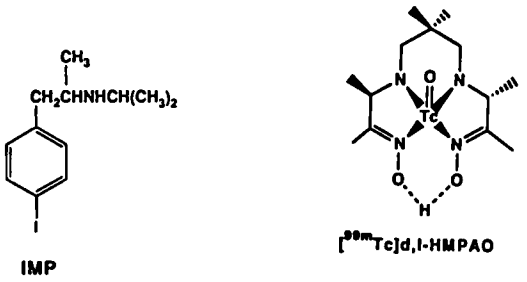

FIG. 1. Organic chemical structures of [^{123}I]IMP and ^{99m}Tc-HMPAO.

As expected, the initial regional brain distributions of IMP and HMPAO will be very similar. Both agents will demonstrate substantial uptake in cortical and subcortical gray matter with lesser uptake in brain white matter. However, because of IMP redistribution, the brain concentrations of these agents will be quite dissimilar beyond the first hour postinjection.

BIODISTRIBUTION AND DOSIMETRY

Aside from the brain, substantial amounts of IMP are concentrated in the lung and liver after injection (*13*). Interestingly, IMP is also concentrated in cells actively producing melanin and has been demonstrated to localize in human melanoma tumors (*14*). For the recommended maximum dose of 6 mCi, dosimetry estimates for IMP are as follows: brain (0.35 rad), lung (0.84 rad), liver (0.78 rad), thyroid (unblocked) (16.2 rad), whole body (0.26 rad), and ovaries (0.26 rad). The thyroid dose can be reduced to under 1 rad by using a thyroid uptake blocking agent such as Lugol's solution or saturated solution of potassium iodide. The d,l isomer of HMPAO is distributed postinjection into the brain, heart, urinary tract, and hepatobiliary system (*10*). Dosimetry estimates for HMPAO based on the maximum recommended dose of 20 mCi are as follows: brain (0.46 rad), liver (0.84 rad), whole body (0.32 rad), and ovaries (0.84 rad). Consequently, with the exception of the unblocked thyroid gland, dosimetry estimates are similar for both agents.

RADIOPHARMACEUTICAL PREPARATION AND QUALITY CONTROL

Because it is commercially tagged and relatively radiochemically stable, IMP requires no in-house preparation or quality control. Single- or multiple-dose vials are ordered from the manufacturer as required and the radiopharmaceutical must be used within 6 hr of calibration.

When HMPAO is to be used, a rather technically demanding protocol is followed for the agent's in-house preparation and quality control. HMPAO is commercially manufactured as a lyopholized "cold kit" with which 10–30 mCi (0.37–1.11 GBq) of ^{99m}Tc in the form of pertechnetate is combined. The pertechnetate should be used within 2 hr of elution from a fresh ^{99}Mo/^{99m}Tc generator, which was eluted at least once within the previous 24 hr. Because the volume of this activity is typically quite small, dilution of the pertechnetate with preservative-free saline to a total volume of 5 ml is usually required. Aseptic techniques and good radiation safety practices must be used throughout the preparation of [^{99m}Tc] HMPAO.

After preparation of HMPAO, administration must be performed within 30 min. However, prior to patient administration, the radiochemical purity of the agent should be determined. This quality control procedure is a three-step process which quantitates the relative amounts of the following three potential impurities: (1) a secondary undesirable complex of ^{99m}Tc-exametazime, (2) free pertechnetate, and (3) reduced hydrolyzed ^{99m}Tc. This three-step process requires ~10–20 min including the chromatography and counting times for the instant thin-layer chromatography (ITLC) strips. Thus, little time can pass between the completion of the quality control and the administration of the HMPAO. A commercial quality control kit has recently become available which has made the overall quality control process slightly less time consuming. However, good planning is necessary in order to complete patient preparation, radiopharmaceutical preparation and its associated quality control within the 30-min time constraint. By following the guidelines of the manufacturer, radiochemical breakdown of the HMPAO will be avoided, resulting in optimum results when using this agent.

SPECT NEUROIMAGING PROTOCOL

Single-photon emission computed tomography (SPECT) neuroimaging with IMP and HMPAO, as in all SPECT imaging, requires technical precision in order to assure high quality images.

When IMP is used, the patient is injected with 4–6 mCi (148–185 MBq) of the agent. This injection must be performed in an isolated room which is free from external stimuli (i.e., light, noise, excessive movement). After injection, the patient remains in this isolated setting for ~15 min, having been instructed to remain quiet with eyes open. After this delay, the patient is placed on a SPECT imaging table, whereupon the patient's head is placed in a head-holder mounted to the table. Then the head is firmly yet comfortably secured in place by a series of velcro straps. Minimizing head movement is critical because of the length of the study, and can be difficult to achieve in certain patients, particularly those afflicted with dementia.

Collimator selection in acquiring IMP studies is complicated by the fact that the principal 159 keV gamma ray of ^{123}I is accompanied by a small but significant amount of high-energy gamma radiation. This high-energy component, which is contributed both by the ^{123}I itself and by certain radioimpurities, reduces spatial resolution and contrast in the image because of penetration of the collimator septa. An older cyclotron technique of producing ^{123}I, the p,2n reaction, resulted in sufficiently large amounts of contaminant high-energy radiation to compel the use of medium-energy collimators. Recently, the p,2n method has been replaced by the p,5n reaction in order to provide relatively impurity-free ^{123}I and to enable the use of lower-energy collimators. However, because of the substantial variation in collimator design from

manufacturer to manufacturer, it is highly recommended that each user test the collimators of his particular gamma camera to determine which performs best by acquiring a series of SPECT studies on a phantom filled with ^{123}I. One should attempt to duplicate the clinical situation as closely as possible. For our camera system, the low-energy general-purpose collimator substantially provides better contrast and resolution than all others, including a long-bore collimator which refers to the longer length of collimator septa or holes especially designed for use with the older variety of ^{123}I preparations.

We use an acquisition zoom factor of 1.7 with an electronic offset to center the image in the lower middle third of the detector area. A 64 × 64 byte mode continuous acquisition is made, acquiring data frames for each 3° over a total 360° acquisition (120 frames). An acquisition time of 30 min should result in a 1–2 million-count study for ^{123}I, depending on the collimator used. A 3–4 hr postinjection delay study may be indicated clinically when using IMP.

As with collimator selection, the selection of the best reconstruction filter is an individual choice that depends on a number of variables, including the personal preference of the image interpreter. By reconstructing an ^{123}I SPECT phantom study with a variety of filters, one can objectively select the filter that best fits his particular needs. The phantom study should be acquired in a manner similar to a clinical study, especially with regard to total counts. Because the number of counts tends to be low, a filter with a smoothing effect is usually desirable. It is important not only to examine the reconstructed slices for features that are known to be present in the phantom (true-positive features) but also for artifacts that do not correspond to reality (false-positives). Generally speaking, a filter that consistently produces even a small number of false-positive features should be avoided. We have found the Parzen filter best for IMP.

HMPAO imaging requires some alteration in imaging techniques, although the basic principles remain constant. For this study 10–20 mCi (370–740 MBq) were administered. The injection of HMPAO is again performed in an isolated environment. The delay in imaging following injection is extended to 1 hr because of the more rapid blood clearance of HMPAO. It should be mentioned that a dynamic flow study and static planar imaging using HMPAO may be useful in visualizing gross abnormalities of perfusion. However, SPECT imaging greatly enhances the ability to make an accurate diagnosis of altered perfusion sites within the brain, especially when the areas of perfusion defects are of limited size. Uniformity maps are applied to the raw projection data prior to reconstruction of the SPECT slices. Again, the patient is placed on the SPECT table and the head secured as previously described. We have found our custom-designed long-bore collimator best for HMPAO studies, although the standard low-energy, high-resolution collimator also provides satisfactory results. A 15–30 min acquisition time should result in a 2.5–5-million count study. Otherwise, the imaging protocol resembles that of [^{123}I] IMP, with the exception that the Hanning filter is used for reconstruction.

Clinical Considerations

Generally, neuroimaging results from IMP and HMPAO are usually very similar. However, on occasion the findings can be discordant (see Ref. 17). In general, functional brain images obtained with either IMP or HMPAO will show abnormalities earlier and more extensively than images from x-ray computed tomography (CT) which primarily depicts anatomic brain information (*15*). In this respect, both IMP and HMPAO neuroimaging can be considered to have high sensitivity for detecting a variety of CNS pathology.

Both agents are extremely safe for use in humans, and even though CT imaging of the brain is also a very safe procedure, there are nevertheless occasional reactions to the iodinated contrast agents often used during CT imaging. However, for IMP it is very important to be certain that the patient to be studied is not taking any type of monoamine oxidase inhibitor medication, as very severe and dangerous elevations in blood pressure have been reported in these individuals after receiving IMP injections (*16*).

During acute cerebral infarction, the blood supply to a region of the brain is abruptly cut off as a result of thrombus formation or embolus occluding a major cerebral artery. In this setting, functional neuroimages obtained with either IMP or HMPAO will typically demonstrate very similar reduced tracer concentration in the region of brain involvement, representing some combination of ischemic and infarcted tissue. In addition, image results from IMP or HMPAO will often reveal a decrease in tracer in the opposite cerebellar hemisphere referred to as crossed cerebellar diaschisis. While both agents are very sensitive for identifying the decreased brain blood flow associated with stroke, there are reports that on rare occasions IMP may show a perfusion defect when HMPAO results are normal and the severity of a particular defect may be greater on the IMP images than the HMPAO images (*17*).

TABLE 1. Relative Advantages and Disadvantages of IMP and HMPAO

HMPAO		IMP	
Advantages	**Disadvantages**	**Advantages**	**Disadvantages**
Ready availability	No redistribution	Redistribution phenomenon	Availability
Can use larger dose	In vitro instability	No prep or quality control	Small imaging dose
Slightly better image quality	Should wait at least 1 hr between injection/acquisition		Cost
Acquisition up to 8–10 hr after injection	Quality control required		

There are instances when results with IMP may be somewhat different from HMPAO in stroke studies. It is felt by some investigators that the phenomenon of IMP redistribution can be used to help separate infarcted regions of the brain from regions of ischemia (*5,18*). Consequently, it may be possible to use IMP to distinguish transient ischemic attacks from cerebral infarction during an acute event. Such a distinction will be critical in the future when more specific therapies become available for stroke patients. Because HMPAO does not redistribute in the brain after initial uptake, this agent cannot be used to differentiate zones of ischemia from infarction. At times, HMPAO images will show increased uptake at the site of acute infarction. This results from the presence of luxury perfusion which represents a condition whereby regional blood flow is increased out of proportion to local metabolic tissue needs. While IMP images will occasionally also depict this phenomenon, typically increased IMP in the region of infarction is seen much less frequently than with HMPAO (*19*).

DEMENTIAS

Dementia represents another major category of neurologic disorders often evaluated with SPECT functional neuroimaging. Multi-infarct dementia and Alzheimer's type dementia are characterized by moderately specific patterns of brain activity on functional neuroimages. In Alzheimer's dementia cases, the typical appearance of reduced activity in the posterior parietal and temporal brain regions is seen both with IMP and HMPAO (*20,21*). Similar imaging results are also found for both agents in cases of multi-infarct dementia where multiple asymmetric focal defects are usually seen in the brain (*21,22*).

SEIZURE DISORDERS

In patients with epilepsy, seizure activity is typically accompanied by increased perfusion and metabolism and, therefore, increased IMP or HMPAO uptake during the seizure (*23,24*). It has been shown that HMPAO images performed in the early period right after the seizure also demonstrate foci of increased perfusion at the site of pathology (*25*). During the interictal or asymptomatic period between seizures both IMP and HMPAO have been used to successfully identify the location of seizure origin in the brain which is depicted at this time as a focus of decreased tracer activity (*25*). The lack of HMPAO redistribution can be used to advantage in seizure disorders because injection can be made during induced seizure activity with imaging performed some time later after seizure activity subsides. This can be of great value to the neurosurgeon when surgical excision is deemed to be appropriate management for the patient with seizures. In addition to stroke, dementia and epilepsy, results from IMP and HMPAO have also been similar for other CNS disorders including various psychiatric illnesses. While it can be seen that these two agents often depict the same pathophysiologic changes in the brain, it is still useful for the clinician to bear in mind the different properties of these radiopharmaceuticals when assessing neuropathology.

SPECIFIC CONSIDERATIONS

Various clinical and technical factors may influence the choice of neuroimaging agent to be used. There are certain advantages for using either agent, which are summarized in Table 1. From a practical standpoint HMPAO has the distinct advantage for clinical use of being available at all times in a kit preparation. In addition, as a result of the larger dose and specific collimation considerations, image quality is often modestly better with HMPAO (Fig. 2). The use of HMPAO requires more technical expertise and overall staff time. This reality may be offset by the better imaging characteristics of ^{99m}Tc versus ^{123}I. The actual imaging time when using HMPAO may be reduced because of the higher count rate achieved. This factor may influence its use in uncooperative or demented patients, where shorter imaging times may be most beneficial. The use of sedatives may become necessary in some cases as deemed appropriate by the medical staff to assure patient compliance.

Costs for both radiopharmaceuticals are relatively high. [^{123}I]IMP in its commercial form costs $200–$250 per patient dose. HMPAO in cold kit form costs ~$150–$180 per vial. The cost of pertechnetate which is added to the vial, plus the costs of the disposables required to prepare and perform quality control on the final preparation adds an additional $10–$20 per vial. It is possible, however, to draw two patient doses from the vial if required.

With the use of these neuroimaging agents on the increase, each institution must refine its technical expertise and design imaging protocols to optimize the results from each of these agents to assure that useful clinical information is gained.

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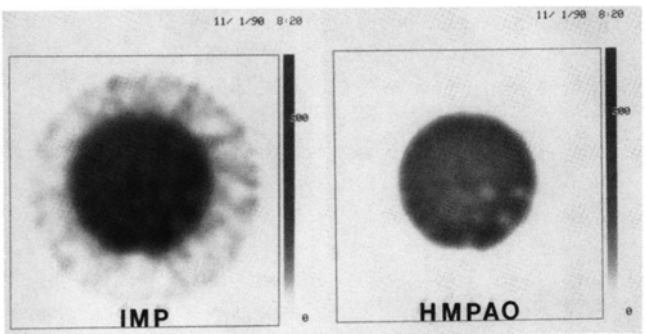

FIG. 2. Comparison of transaxial slices through the solid rods section of a Jasczak phantom filled with ^{123}I (left) and ^{99m}Tc (right). Image acquisition closely approximates clinical conditions. It can be seen that resolution is somewhat better for HMPAO.

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