INVESTIGATIVE NUCLEAR MEDICINE

A Comparison of Two Cerebral Perfusion Tracers, N-Isopropyl I-123 p-Iodoamphetamine and I-123 HIPDM, in the Human

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Both N-isopropyl I-123 p-iodoamphetamine (IMP) and I-123 HIPDM have been advocated as radiotracers for assessing regional cerebral perfusion. We compared the biodistribution of the two tracers in 19 patients without evidence of neurological disease. Following intravenous injection, both tracers accumulated initially in the lung. Early after injection the fraction of the total brain uptake was higher for I-123 HIPDM than for I-123 IMP. The peak brain activity for I-123 IMP was higher than for I-123 HIPDM. Brain activity was unchanged with both tracers between 30 and 60 min after injection. Tomographic images were similar in appearance for both tracers. No eye uptake greater than background was observed with either tracer in any patient at 2, 24, and 48 hr. I-123 IMP is superior for tomographic imaging because of its higher brain uptake, whereas I-123 HIPDM may be superior for studies performed during rapid changes in blood flow.

A family of recently developed I-123-labeled amines have accumulated in the brain proportional to cerebral blood flow and are retained sufficiently long to permit cerebral imaging (*1–4*). This development promises to bring into general medical practice the remarkable diagnostic advances that hitherto have been limited to the small number of centers that can afford the costly on-site cyclotrons and technical support required for positron emission tomography (*5*). Two of these tracers, the monoamine, N-isopropyl-p-[^{123}I]iodoamphetamine (IMP) and the diamine, N,N,N'-trimethyl-N'-[2-hydroxyl-3-methyl-5-iodobenzyl]-1,3-propanediamine, I-123 (HIPDM) have already shown promise in a number of neurologic disorders, including cerebral vascular disease and epilepsy (*6–11*).

While both radiopharmaceuticals concentrate in the brain proportional to blood flow and are retained within the brain for some time after injection (*3*), differences in their biodistribution might affect their relative at-

tractiveness in the clinical setting. We therefore determined the biological behavior of the two tracers after intravenous injection in man, with particular attention to the characteristics of brain uptake.

METHODS

N-isopropyl-p-[^{123}I]iodoamphetamine (I-123 IMP) was prepared commercially,* using a technique described previously (*4,7*). Briefly, purified, carrier-free Na^{123}I was mixed with N-isopropyl-p-iodoamphetamine and heated at 150° for 30 min. The reaction mixture was then extracted with ethyl ether, washed, purified, dried, taken up in 0.3 N HCl, neutralized with 0.03 N NaOH, diluted with normal saline, and sterilized.

Radiochemical purity was checked with thin-layer chromatography using silica gel-60 plates with methanol/chloroform/glacial acetic acid (5:85:1 vvv) as eluent. The proportion of I-124 present was checked by counting the radiotracer on a Canberra multichannel analyzer with a Ge(Li) detector.

N,N,N'-trimethyl-N'-[2-hydroxyl-3-methyl-5-[^{123}I]-

iodobenzyl]-1,3-propanediamine (I-123 HIPDM) was prepared from a nonradioactive kit (3) and Na¹²³I was supplied commercially.

Sodium iodide (I-123) was mixed with acidified nonradioactive HIPDM and heated, with exchange of radioiodine into the HIPDM, producing I-123 HIPDM. The pH was adjusted by adding NaOH-fortified buffer, and the solution was sterilized by passage through a 022-μ filter. Radiochemical purity was checked with thin-layer chromatography using silica gel-60 plates and a solvent system with $CHCl_3/EtOH/NH_4OH$, 8:2:0.8 vvv), as the eluent. The proportion of I-124 was checked as described above for I-123 IMP.

A total of 19 patients without clinical or laboratory evidence of cerebrovascular or neurologic disease were studied. All patients were hospitalized for reasons unrelated to CNS complaints, and voluntarily participated in this study after giving written informed consent.

The in vivo time courses of the two radiotracers in the brain, lung, liver, and bladder were measured over the first 24 hr in one patient. Two millicuries of I-123 HIPDM were injected intravenously. Imaging was performed with a large-field-of-view Anger scintillation camera with a medium-energy collimator (3000-hole, 44–400 keV), and the pulse-height analyzer, with 20% window, peaked symmetrically over the 159-keV photopeak of I-123. Data were collected on a computer using standard software. Imaging began within the first 4 min of injection. The patient was positioned initially for an anterior view of the brain. After 45 sec of data collection, the patient was repositioned (15 sec) for an anterior view of the lungs (45 sec), then repositioned (15 sec) for an anterior view of the liver (45 sec), and finally repositioned (15 sec) for an anterior view of the bladder (45 sec). This 4-min sequence was repeated continuously for the first hour and at 10-min intervals for the second hour. A square region of interest was placed over each of the four organs on the initial images, and counts were collected from those and subsequent images. The study was repeated 2 mo later in the same subject using 2 mCi of I-123 IMP with a comparable quantity of I-124 contamination.

In five patients injected with 2.0–4.3 mCi of I-123 IMP, and five patients injected with 1.3–5.9 mCi of I-123 HIPDM, Anger-camera imaging began immediately after injection. The patients were positioned in the anterior projection so that the entire brain and as much of the upper lung fields as possible were included in the field of view. Data were collected in 60-sec frames from the time of injection up to 60 min. Irregular regions of interest were placed over the brain and the lungs. Time-activity curves were then constructed for each of these organs. The ratios of brain uptake and lung clearance were normalized to the maximum activity recorded in the organ during the 60 min of data recording for each patient.

In five patients injected with 5–5.6 mCi of I-123 IMP, and three patients injected with 5–5.6 mCi of I-123 HIPDM, emission computed tomography was performed using a multidetector scanning brain system (6,12). The studies were all performed in dual-channel mode with the lower-energy pulse-height window set at 135–185 keV (bracketing the I-123 peak) and the higher-energy window set at 310–360 keV. Transaxial tomographic slices were obtained along a plane 2 cm above the orbitomeatal line. Imaging began 30 min after injection. Each image required 5 min, and imaging continued at the same level until 1 hr after injection. The total number of counts in each image was determined after correcting for I-124 scatter using a high-energy mask described previously (6). Time-activity curves were constructed for brain activity in each of the eight patients.

In five of the above patients injected with I-123 HIPDM and five of the patients injected with I-123 IMP, we obtained Anger-camera images of the head in the anterior and lateral projections at 2, 24, and 48 hr, to ascertain whether eye uptake could be observed in concentrations above the brain and soft-tissue background.

RESULTS

In the 19 patients studied, the amount of I-124 contamination (I-124/I-123) at the time of injection was (3.4 ± 0.1)% (s.e.m.; range 3.0–4.1%) for I-123 IMP, and (3.3 ± 0.1)%, range 3.0–3.6%, for I-123 HIPDM.

Following an intravenous injection, both I-123 IMP and I-123 HIPDM accumulated initially in the lung. Lung clearance was faster for I-123 IMP (Figs. 1, 2). By 30 min, the lung activity was (43.6 ± 5.7)% (s.e.m.), of the initial maximum lung activity for I-123 IMP and (64.0 ± 9.1)% for I-123 HIPDM. The lung clearance of I-123 HIPDM remained slower than that of I-123 IMP throughout the period of observation, so that by 60 min the lung activity was (33.0 ± 4.8)% of the peak lung activity for I-123 IMP and (47.8 ± 8.1)% for I-123 HIPDM. The range of lung clearance was wide for both I-123 IMP and I-123 HIPDM, so that lung clearance at 30 min ranged from 34.6–65.2% of the initial peak ac-
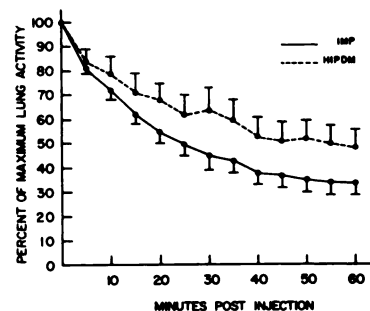

FIG. 1. Lung clearance of I-123 IMP and I-123 HIPDM, normalized to peak initial lung activity.
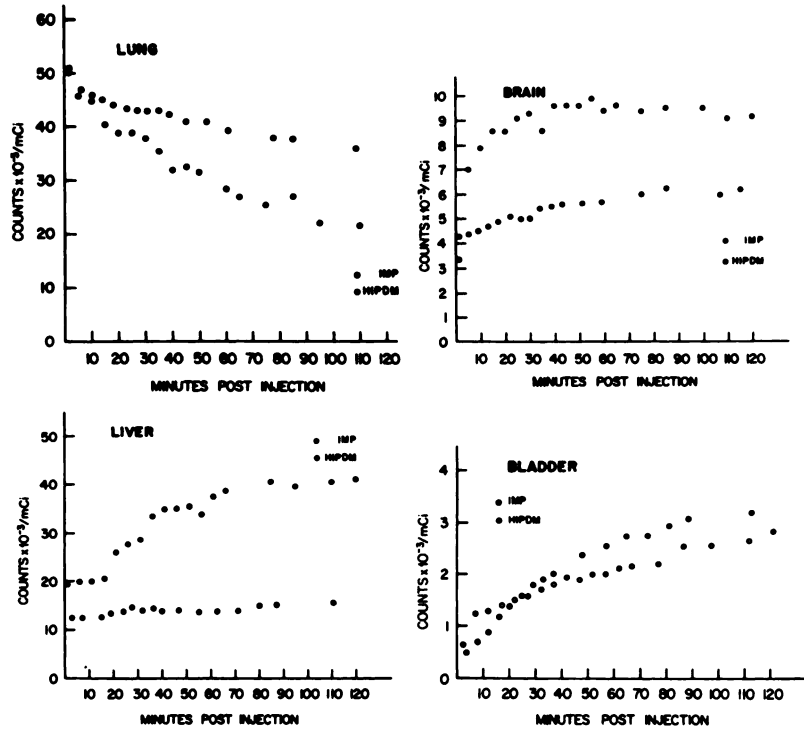
FIG. 2. Pulmonary, brain, hepatic, and bladder time-activity curves in subject injected intravenously with both I-123 IMP and I-123 HIPDM. (n = 5 patients for each group).

tivity in the five patients injected with I-123 IMP, whereas the range was 34.6–87.3% in the five patients injected with I-123 HIPDM.

The initial fraction of tracer extracted and retained by the brain (as a fraction of the maximum brain activity recorded during the first hour) was higher for I-123 HIPDM than for I-123 IMP (Fig. 3). By 2 min after injection, the brain activity was (45.0 ± 4.0)% of peak for I-123 IMP compared with (73.6 ± 3.0)% for I-123 IMP. This difference disappeared by 30 min after injection.

The percent injected dose of I-123 IMP extracted and retained by the brain was higher for I-123 IMP in all three of the comparison studies: (a) In the subject injected with both tracers, peak brain activity of I-123 HIPDM was 58.7% of the I-123 IMP peak activity level (Fig. 2); (b) in those studied with the Anger camera the corresponding figure was 51.6%; and (c) in patients

studied by ECT the peak I-123 HIPDM activity was 57.9% of the I-123 IMP peak activity. Furthermore, brain activity remained constant with either I-123 IMP or I-123 HIPDM between 30 and 60 min after injection (Fig. 4).

The peak liver count rate was 2.5 times the peak brain count rate for I-123 HIPDM, and 4.3 times that for I-123 IMP (Fig. 2). The time-activity curves also differed between liver and brain. For I-123 IMP the rate of uptake was gradual, with increasing liver activity throughout the course of observation; for I-123 HIPDM, uptake was prompt, with less than 13.2% increase in activity between 20 min and 2 hr. Peak liver activity for I-123 IMP was 2.6 times that of I-123 HIPDM.

Tomograms were similar in appearance for the two tracers (Fig. 5). The activity concentration was highest in the strip of cortex along the convexity of the cerebral
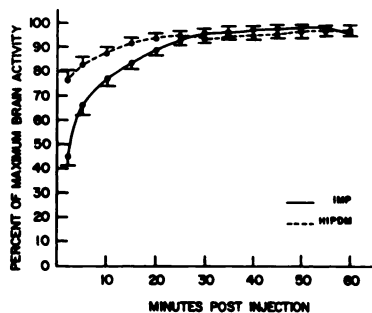

FIG. 3. Brain time-activity curves for I-123 IMP and I-123 HIPDM, normalized to maximum brain activity observed during first 60 min after injection. (n = 5 patients for each group).
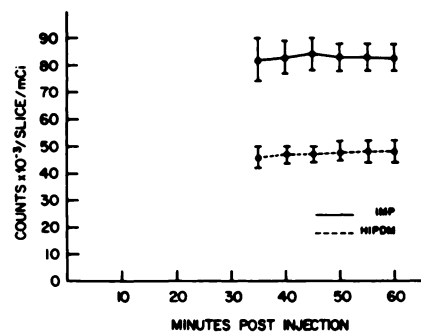

FIG. 4. Brain activity for I-123 IMP and I-123 HIPDM measured by emission computerized tomography at plane 2 cm above orbito-meatal line. (n = 5 patients for I-123 IMP, s.d., and 3 patients for I-123 HIPDM, range).
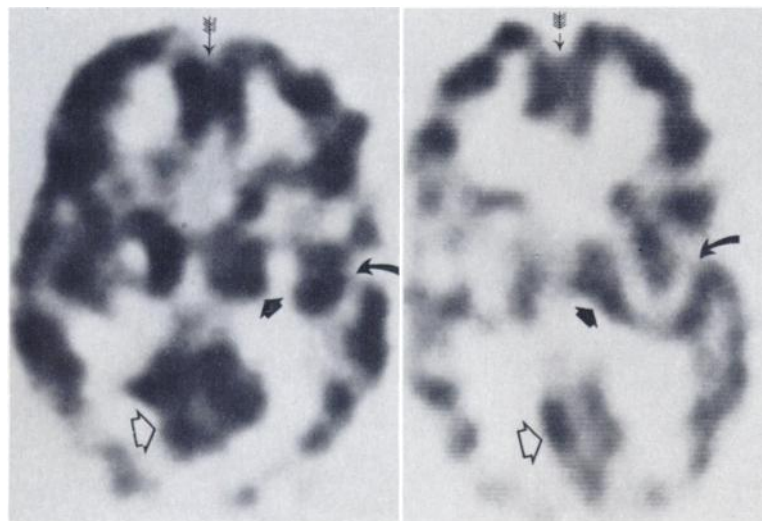
FIG. 5. Tomograms obtained with I-123 IMP (left) and I-123 HIPDM (right), both with high cerebral activity in cortical gray matter, basal ganglia, and thalamus. Transaxial sections were obtained from plane 2 cm above orbitomeatal line; frontal lobes are at upper part of image and occipital lobes at lower part. Thalamus and basal ganglia (arrow), Sylvian fissure (curved arrow), visual associative area (open arrow), interhemispheric fissure (frontal lobe) (feathered arrow).

hemispheres (cortical gray matter) and in the region corresponding to the basal ganglia and thalamus. The interhemispheric and sylvian fissures could be resolved using both agents, as could the major gyral architecture of the cerebral cortex, which appeared as an undulating border along the periphery of the image.

With Anger-camera imaging, brain activity was still prominent at 2 hr with both tracers. There was substantial clearance of activity from the brain at 24 and 48 hr. No eye concentrations greater than background were observed in any patient at 2, 24, or 48 hr after injection with either tracer (Fig. 6).

DISCUSSION

Recently a number of amines that meet the two requirements for brain imaging—high blood-brain barrier permeability and retention in the brain parenchyma—have been synthesized and labeled with iodine-123. Winchell and his colleagues found that N-isopropyl-p-[^{123}I]iodoamphetamine was the most promising of the monoamines that they studied (2). This group of compounds penetrate the blood-brain barrier due to free diffusion of the unionized lipophilic form of the compound. Once inside the brain parenchyma, they are retained either by nonspecific binding or by metabolism

into an ionized lipophobic form. Another family of compounds, the diamines, have been synthesized and studied by Kung et al. (3). Of the compounds in this group that were tested, the highest brain localization in animals was found with I-123 HIPDM. It has been suggested that the retention of this family of compounds in the brain is based on a different mechanism, pH shift (3,13), and that these diamines take advantage of the pH gradient that exists between blood (pH 7.4) and brain (pH 7.0). At high pH, they are neutral and lipid-soluble, and can diffuse freely into cells, but at lower pH they become charged and can no longer diffuse out. The pH-gradient hypothesis, which led to the development of these tracers, does not account for their very high brain-to-blood activity ratios (14). As a result, rapid metabolism or nonspecific binding may account at least in part for brain retention of diamines as well as the monoamines.

HIPDM and IMP have similar characteristics. For example, the profiles of the partition coefficients are similar between pH 7.0 and 7.4 for HIPDM and IMP, with slopes of 3.5 and 2.8, respectively (3). The lipid-solubility is high for both tracers, with partition coefficients greater than two over a wide range of pHs (octi-nol:water). The brain uptake in the rat is also similar for two agents.
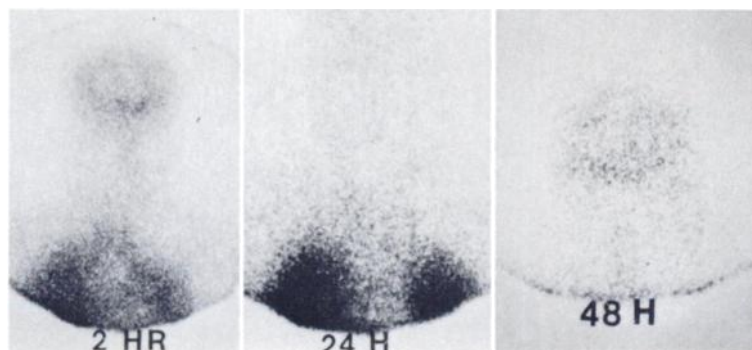

FIG. 6. Anger camera images (similar for two agents) of head obtained in anterior projection at 2 hr, 24 hr, and 48 hr after injection. Eyes do not concentrate tracer to greater extent than brain or background.

While we have found that there is a good deal of similarity between the two tracers in man, there are some differences that may bear on the choice of radiopharmaceutical for brain perfusion imaging. Brain activity of IMP is almost twice as high as that for HIPDM during the time at which imaging would be performed—between 20 and 60 min after injection. These differences are not due to free iodide, which was less than 5% in all of our studies. We cannot tell from our data whether the differences are due to intrinsic properties of IMP and HIPDM or to labeling of impurities using the method of Kung and Blau (3).

As a result of its greater affinity for the brain, IMP may be more attractive for tomographic imaging, where the higher brain uptake may be useful due to the limited sensitivity of rotating gamma cameras. It is likely that the standard injected dose for I-123 cerebral perfusion tracers will be 3 mCi or less, due to the expense of I-123 and the dosimetry of the tracers (15), further increasing the need for optimizing brain uptake. Also, I-124 contamination, with its accompanying high-energy gamma emissions, will hamper accurate data reconstruction if counting statistics are not adequate to allow accurate subtraction of the high-energy gamma background. While I-123 may ultimately be produced entirely by the p, 5n method, eliminating I-124 contamination, much of the I-123 currently available in the United States is produced by the p, 2n reaction and contains up to 4% of I-124 contamination.

Both tracers maintain a steady state in the brain over a period sufficiently long to permit static imaging. The steady state is maintained long enough so that tomographic imaging using the rotating gamma camera can be performed between 20 and 60 min after injection, without significant redistribution of the tracer.

The time it takes for the tracer to accumulate in the brain may have a bearing on the development of techniques to measure cerebral blood flow quantitatively. The ideal perfusion tracer would pass immediately through the lungs, would be extracted completely by the brain during the first intravascular transit, and would remain in the brain without redistribution. Both I-123 IMP and HIPDM have blood-brain extraction fractions of over 90% (3,4) and, as we have shown, they remain in the brain for at least an hour after injection.

While the kinetics of brain uptake and release cannot be determined from our data, we can make qualitative predictions concerning the duration of the steady state in cerebral blood flow required to capture a physiologic state or pharmacologic intervention. Thus, the accumulation of I-123 HIPDM in the brain was more rapid than that of I-123 IMP, reaching over 75% of the 60-min peak brain activity by 2 min after injection, compared with 45% for I-123 IMP. As a result, the steady state for cerebral blood flow need not be as long with I-123 HIPDM as with I-123 IMP. For example, patients with

epilepsy can be injected at the time of seizure activity and studied later after the seizure has been brought under control. Assuming that the seizure lasts only a short time and that the increase in tracer concentration is linearly related to flow in patients with epilepsy, brain activity will reflect blood flow at the time of a seizure more closely with I-123 HIPDM than with I-123 IMP.

Neither tracer accumulates in the eye in concentrations greater than background. IMP concentrates in the eyes of a number of animals, including the rhesus and cynomolgus monkey (15). Uptake appears to be related to active melanin synthesis (16) and probably does not occur in the human eye because melanin synthesis ceases in embryo.

In summary, I-123 IMP appears to be the preferable tracer for standard planar and tomographic imaging because of higher brain uptake. I-123 HIPDM reaches peak brain activity rapidly and may be the preferable of the two tracers for quantitative studies and for studies with rapid changes in cerebral blood flow.

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