Technetium-99m-d,1-HM-PAO: A New Radiopharmaceutical for Imaging Regional Brain Perfusion Using SPECT—A Comparison with Iodine-123 HIPDM

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A new radiopharmaceutical, technetium-99m hexamethylpropyleneamine oxime (^{99m}Tc-d, 1-HM-PAO), has been reported to cross the blood-brain-barrier and to distribute in brain in proportion to regional blood flow. This study reports brain imaging obtained with ^{99m}Tc-d,1 HM-PAO in 20 subjects; seven without evidence of cerebral disease and 13 with cerebrovascular disorders. In 16 patients comparative data were available with N,N,N′-trimethyl-N′-(2-hydroxy-3-methyl-5-iodobenzyl)-1,3-propanediamine (^{123}I]HIPDM). Technetium-99m-d,1-HM-PAO is retained sufficiently long to allow single photon emission computed tomography (SPECT) with widely available rotating gamma camera systems. The kinetics demonstrated a rapid brain uptake and prolonged retention of activity in cerebral structures. Good tomographic images are obtained with much higher uptake in gray than in white matter. Blood flow maps are comparable to those achieved with [^{123}I]HIPDM and established strokes were clearly seen, with similar details as in HIPDM studies. Delayed studies showed that the distribution in the brain remained virtually unchanged. Technetium-99m-d,1-HM-PAO imaging appears particularly promising in routine examination of patients with cerebrovascular disorders.

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Single photon emission computed tomography (SPECT) using ^{123}I-labeled amines has been used for some years to map regional cerebral blood flow in man (*1–5*). The major drawbacks of ^{123}I, however, are cost and limited availability. Technetium-99m has none of these disadvantages and several new rCBF tracers based upon this radionuclide have been proposed (*6–9*). The main requirements for rCBF evaluation with SPECT are that the radiopharmaceutical cross the intact blood-brain-barrier (BBB) and distributes proportional to blood flow. The tracer should retain a fixed regional distribution in the brain for a period sufficient to permit image acquisition. For a rotating gamma camera system, this is typically 20–30 min.

Following the discovery that the ^{99m}Tc complex of propyleneamine oxime (PnAO) forms a neutral lipophilic complex (*10*) and demonstrates transient flow-related brain uptake in rats (*10*), dogs (*11*), and man (*12*), a large number of derivatives of PnAO were synthesized at Amersham International Laboratories* (*13*).

The ligand which combined the best overall features of high brain uptake, fixed regional distribution within the brain, and ease of radiopharmaceutical preparation was the d,1 isomer of hexamethyl propyleneamine oxime (d,1 HM-PAO) (*14*).

The aim of this study is to present our initial experience with d,1 HM-PAO for SPECT-brain imaging in patients suffering from cerebrovascular disease. Moreover, a direct comparison, between ^{99m}Tc-d,1 HM-PAO and ^{123}I-labeled N,N,N′-trimethyl-N′-[2-hydroxy-3-methyl-5-iodobenzyl]-1,3-propanediamine ([^{123}I]HIPDM) was performed.

MATERIALS AND METHODS

Technetium-99m-d,1 HM-PAO was prepared from a nonradioactive kit (Ceretec).* The vials were reconsti-

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tuted with 5.0 ml of saline containing a maximum of 30 mCi [^{99m}Tc]sodium pertechnetate. Iodine-123 HIPDM was procured commercially,[+] ^{123}I being produced by the (p,5n) reaction.

Analysis of Technetium Complexes

A combination of three chromatographic systems was used to measure the radiochemical composition of the ^{99m}Tc complex of d,l-HM-PAO. Ten-microliter test samples were applied 2.5 cm from the base of two silica gel (ITLC/SG[‡], 2 × 20cm) and one Whatman No. 1 (2 × 30cm) chromatographic strips. Immediately after the application of the sample, the strips were subjected to ascending chromatography. The two ITLC/SG strips were developed in methylethyl ketone (MEK) and 0.9% saline, and the Whatman No. 1 strip was developed in 50% aqueous acetonitrile. After development, the strips were removed, dried, and the radioactivity distribution determined.

The percentage of the lipophilic complex of d,l-HM-PAO was calculated as the difference between the percentage activity at the solvent front in the MEK system, less the percentage at the solvent front in the saline system (pertechnetate). Activity remaining at the origin on the aqueous acetonitrile system provided the percentage of reduced, hydrolysed technetium. The remaining radioactivity constitutes a secondary, less lipophilic complex of d,l-HM-PAO.

Clinical Studies

The studies were carried out with a conventional rotating gamma camera.[§] Data were obtained from 64 projections into a 64 × 64 matrix, using a high resolution low-energy collimator. Intravenous administration of the radiopharmaceutical was conducted in a quiet room with dimmed lights; the patient was supine with his eyes closed and his ears plugged for 15–30 min. With the ^{99m}Tc agent data collection was started 10–30 min after the injection of 0.5-1 GBq. The total acquisition time was 15 to 30 min during which time 3–5 million counts were collected. Iodine-123 HIPDM imaging began 20 to 40 min after injection of 0.2 to 0.3 GBq. The tomographic studies lasted between 30 and 60 min during which period 2.5 to 5 million counts were collected. Nine repeat studies were performed with ^{99m}Tc-d,l-HM-PAO at 4 to 6 hr after injection.

In five patients imaging began immediately after HM-PAO injection. Each image (20 sec per frame) was collected over 10 min. The entire brain and the upper lung fields were included in the field of view. In one case the lung and the abdominal area were included. Irregular regions of interest (ROIs) were placed over organs and time-activity curves were then constructed.

Anterior views of the lung and abdominal organs were obtained in five patients at 10 min, 1 hr, and 4 hr after injection to image the distribution and excretion of ^{99m}Tc-d,l-HM-PAO.

All data were corrected for attenuation and the tomographic data were reconstructed using a filtered back-projection algorithm. Transverse, coronal and sagittal reconstructions (2 pixels slice) were examined by visual inspection for qualitative image interpretation. For semiquantitative analysis, five symmetrical ROIs were drawn on two middle transverse slices, matching the area of basal ganglia and the perfusion territories of the middle cerebral artery in anterior and posterior segments. The shape of these regions was identical for each patient. Right to left ratios were calculated from the counts in these ROIs. The ratio of count density over low uptake areas relative to the contralateral area were calculated. Gray-to-white matter ratios were calculated on a middle transverse slice considering 4 × 4 pixel ROIs over the insula area (gray matter) and over the anterior periventricular area (white matter).

All results are reported as mean ± standard deviation. A total of 20 subjects were studied: seven controls without clinical evidence of cerebrovascular or neurologic disease and with a normal transmission computed tomography (TCT) and EEG examination; seven stroke patients and six patients with transitory ischemic attacks (TIA) or diffuse cerebral vascular insufficiency. In 16 of these subjects [^{123}I]HIPDM single photon emission computed tomography (SPECT) studies were performed with a between-study interval of 2 to 4 days.

RESULTS

Addition of [^{99m}Tc]pertechnetate to the freeze-dried formulation produces a lipophilic complex of d,l-HM-PAO in >90% yield immediately after complex formation. Other observed components are a less lipophilic ^{99m}Tc complex of d,l-HM-PAO and very small amounts of reduced hydrolyzed technetium and pertechnetate. There is a slow conversion of the primary complex to the less-lipophilic complex. In the clinical results, the brain time-activity curve demonstrated the rapid uptake of ^{99m}Tc d,l-HM-PAO into the brain. The maximal count rate was reached 30–40 sec after the injection. By 2 min after injection the brain activity decreased to 91 ± 1–9% of the peak value and then remained constant throughout the period of observation.

Technetium-99m-d,l-HM-PAO showed no selective concentration in the lung. Liver and kidney uptakes were high and the tracer rapidly appeared in the gallbladder and intestines.

On the brain planar images, there was significantly less background with the ^{99m}Tc agent than with HIPDM: 20.5 ± 5.6% (n = 8) compared with 30.5 ± 3.0% of total counts per projection.

In control subjects, SPECT images demonstrated selective uptake of the ^{99m}Tc-d,l-HM-PAO complex in areas corresponding anatomically to cortical gray mat-

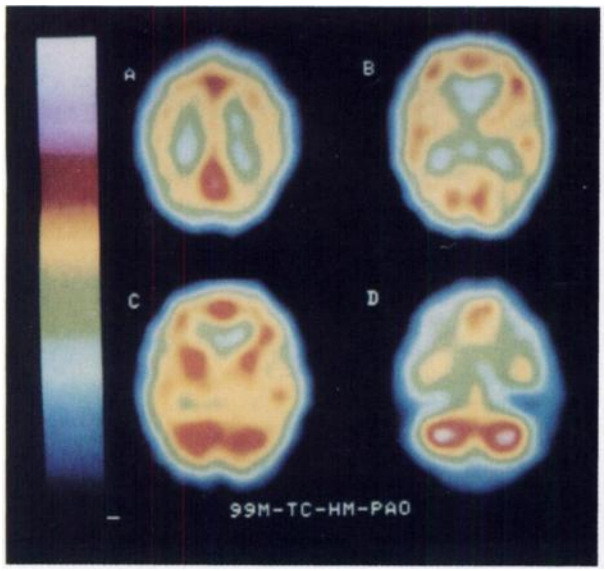

FIGURE 1
Normal subject. A: Frontal and parietal lobes. Interhemispheric gray matter. B and C: Frontal, temporal and occipital cortex. Basal ganglia are visualized. D: Cerebellum and temporobasal region. (Transverse slices of 2 pixels thickness)

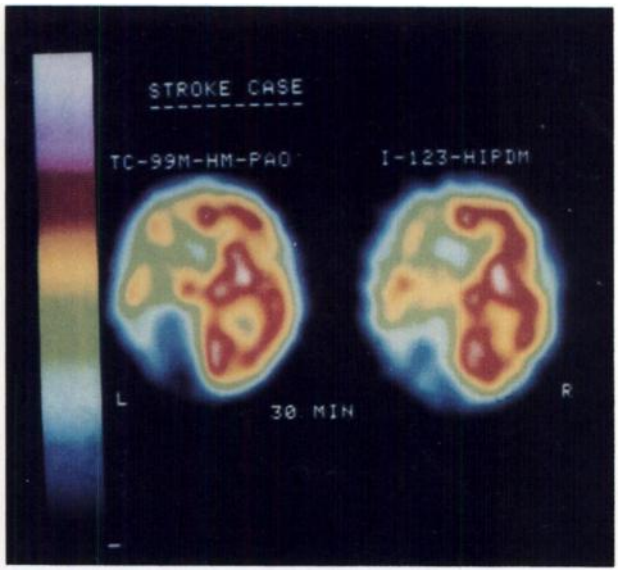

FIGURE 2
Stroke patient. Decreased activity over left hemisphere. Markedly decreased activity over left occipital region. Similar findings are observed with ^{99m}Tc-HM-PAO and with [^{123}I]HIPDM

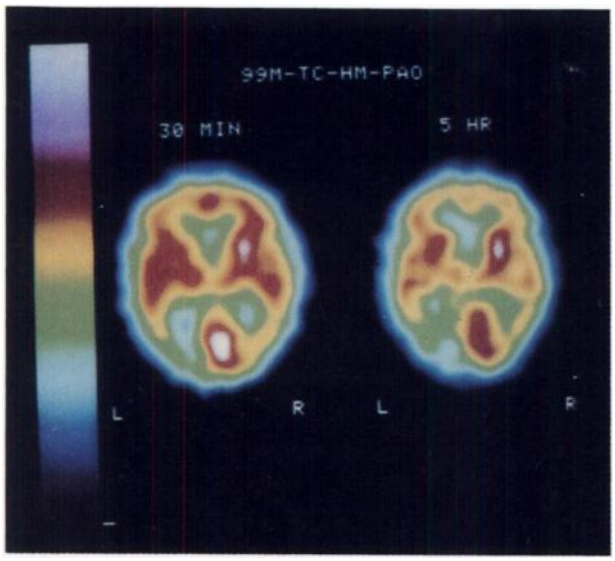

FIGURE 3
Transverse slice 30 min and 5 hr after injection of ^{99m}Tc-HM-PAO. Initial pattern of isotope distribution was virtually unchanged

ter (Fig. 1). Activity was visualized along the convexity of frontal, temporal, parietal and occipital lobes and along the interhemispheric fissure. The basal ganglia were also clearly delineated. The region between the basal ganglia and the convexity had less activity and corresponded to cortical white matter and to the ventricular system. The cerebellar hemispheres could be seen at the base of the brain. This pattern of ^{99m}Tc-d,l-HM-PAO distribution within the brain was closely similar to that obtained in the HIPDM investigations (Fig. 2). The contrast was equivalent for both tracers.

For the ^{99m}Tc agent the gray-to-white matter ratio was 1.77 ± 0.19 (n = 7) at 1 hr and 1.71 ± 0.24 (n = 7) at 5 to 6 hr. The total brain activity was found to decrease slowly from the first hour up to 5–6 hr (8.6% decrease, decay corrected).

Ratios for symmetrical right to left ROIs are given in Table 1 for control subjects; R/L ratios are close to 1 with small standard deviation.

Of the seven stroke patients, five showed perfusion defects involving the frontal, temporal and parietal lobes with variable extension into the occipital lobe and the basal ganglia. One patient had posterior cerebral infarction with defect limited to the occipital lobe. One patient had a normal TCT study and a normal SPECT study. Of the six cases with TIA, two were positive in the ^{99m}Tc study and one of these was abnormal on TCT examination.

In the eight abnormal cases, excellent agreement was found between d,l-HM-PAO tomograms and HIPDM

TABLE 1
Normal Values: ^{99m}Tc-HM-PAO Brain Distribution

N = 7	Mean	s.d.
SPECT right/left ratios		
Middle cerebral artery		
Anterior-inferior	1.000	0.019
Anterior-superior	1.014	0.020
Posterior-inferior	0.982	0.032
Posterior-superior	1.000	0.049
Area of basal ganglia	0.996	0.025

tomograms when both were expressed as a ratio of the count densities in the diseased area (low uptake) versus the contralateral (normal) area. In two cases, the degree of asymmetry was the same for the two agents. In six cases, the asymmetry (diseased-to-nondiseased ratio) was a little more marked on the HIPDM images (ratio = 0.863 ± 0.087) than on the HM-PAO images (ratio = 0.89 ± 0.080). In comparing early and late maps, this asymmetry decreased with time more rapidly on the HIPDM tomograms than on the HM-PAO tomograms; over the first 6 hr only slight variations were seen on the ^{99m}Tc images (Fig. 3). Furthermore, in two of seven cases with stroke, low ^{99m}Tc-d,l-HM-PAO uptake was observed in the contralateral cerebellar hemisphere ("crossed cerebellar diaschisis").

DISCUSSION

The diagnosis of cerebral functional abnormalities has received a fresh impulse from the introduction of the radiolabeled amines isopropyl-^{123}I-iodoamphetamine (IMP) and [^{123}I]HIPDM. SPECT with these amines complements the findings of tissue morphology and may therefore enable the diagnosis of perfusion disorders not revealed by TCT.

In a recent study, we have confirmed the usefulness of HIPDM studies for the assessment of cerebral perfusion in patients with vascular accidents and in the objective documentation of the effectiveness of surgical interventions such as endarterectomy (*5*). A ^{99m}Tc-labeled radiopharmaceutical is the tracer of choice for routine application because it is always available, cheaper than ^{123}I and has better imaging characteristics than most ^{123}I preparations. Recent studies have demonstrated that HM-PAO does cross the blood-brain-barrier and is retained in the brain tissue for several hours, such that its distribution reflects regional cerebral blood flow (*15–18*). This time is long enough to permit tomographic imaging using conventional rotating camera systems.

In the present study, comparing the two tracers ^{99m}Tc-d,l-HM-PAO and [^{123}I]HIPDM, we have found that tomographic images were very similar in control subjects. In patients with cerebrovascular disease, the low flow areas were equally well detected by both tracers.

In some aspects, ^{99m}Tc-d,l-HM-PAO seems more advantageous than HIPDM. First, the short time it takes for the ^{99m}Tc-d,l-HM-PAO to accumulate into the brain and its long retention time without appreciable change in the gray-to-white matter ratio can be useful properties in order to capture a steady state in cerebral blood flow at the time of a rapid physiological or pathological event. Second, the lower background in brain projections must potentially improve the quality and contrast of the reconstructed tomogram. Higher background in HIPDM studies is probably due to prominent activity of [^{123}I]HIPDM in the lung and to the 2% of higher energy photons of ^{124}I.

In summary, ^{99m}Tc-d,l-HM-PAO shows considerable promise for cerebral blood flow tomographic imaging using commercial single-head rotating gamma cameras. The results are in good agreement with those reported for ^{123}I-labeled amines. This new ^{99m}Tc radiopharmaceutical offers a number of advantages. It is more convenient to use, and daily availability provides the possibility for repeat studies. Its superior imaging characteristics should permit the detection of changes in blood flow.

Technetium-99m-d,l-HM-PAO has the potential for becoming a very useful tool for the routine investigation of patients with cerebral disease.

FOOTNOTES

* Amersham International plc, Buckinghamshire, UK.
† I.R.E., Fleurus, Belgium.
‡ Gelman Instrument Company, Ann Arbor, MI.
§ General Electric Medical Systems (400 AT), Milwaukee, WI.

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