Dynamic SPECT with Technetium-99m HM-PAO in Meningiomas–A Comparison with Iodine-123 IMP

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Technetium-99m hexamethylpropyleneamine oxime ([^{99m}Tc]HM-PAO) has recently been introduced as an alternative to N-isopropyl-p-[^{123}I]iodoamphetamine ([^{123}I]IMP) for measurement of regional cerebral blood flow. This study compares dynamic SPECT studies using the two tracers in seven patients with meningiomas. Regions of interest were placed over the lesion and contralateral homologous presumed normal area. The counting-rate ratio for the lesion to the contralateral homologous area (L/N ratio) was then calculated in the first image. L/N ratios of [^{99m}Tc]HM-PAO single photon emission computed tomography (SPECT) were lower than those of [^{123}I]IMP SPECT, particularly in hypervascular meningiomas. Furthermore, time-activity curves showed that the washout of [^{99m}Tc]HM-PAO in the tumors was very slow or incomplete, preventing an accurate assessment of vascularity of meningiomas with [^{99m}Tc]HM-PAO, as is generally possible with [^{123}I]IMP.

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Widespread single photon emission computed tomography (SPECT) imaging facilities have promoted the development of new radiopharmaceuticals for regional cerebral blood flow (rCBF) imaging. First, N-isopropyl-p-[^{123}I]iodoamphetamine ([^{123}I]IMP) was introduced in 1980 (*1,2*) and it has been used widely to map relative rCBF images with SPECT (*3–6*). Recently, several new lipophilic technetium-99m (^{99m}Tc) complexes have been described as alternatives to [^{123}I]IMP for rCBF imaging (*7–10*). In particular, ^{99m}Tc-(d,l)-hexamethylpropyleneamine oxime ([^{99m}Tc]HM-PAO) shows good brain retention (*11–16*) and its clinical use has spread very rapidly. In brain tumors, however, both [^{123}I]IMP (*17–19*) and [^{99m}Tc]HM-PAO (*20*) have failed to demonstrate their rCBF because many brain tumors have no retention mechanism of these tracers. On the other hand, we have already demonstrated the usefulness of the dynamic SPECT with [^{123}I]IMP in evaluating the vascularities of meningiomas (*21*). The purpose of our present study is to compare the kinetic behavior of [^{99m}Tc]HM-PAO in meningiomas with that of [^{123}I]IMP.

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MATERIALS AND METHODS

Patient Selection

This study includes seven patients with meningiomas, four males and three females, aged 42 to 86 yr (median age 59 yr). All patients underwent angiographies and x-ray computed tomographic (CT) scans with and without i.v. administration of contrast medium. Six patients underwent total resection of the tumors and their histologic diagnoses were confirmed; the remaining patient's diagnosis was made by x-ray CT scan and angiography.

Patient Preparation

Measurements of rCBF were performed with SPECT using [^{123}I]IMP and [^{99m}Tc]HM-PAO. Iodine-123 IMP was obtained from Japan Mediphysics (Takarazuka, Japan) on the day of the examination. It was free of ^{124}I and contained at most 4.5% of ^{125}I. While, [^{99m}Tc]HM-PAO was prepared from a nonradioactive kit (Amersham International, Buckinghamshire, UK) according to the method described by Neirinckx et al. (*16*). The preparation of [^{99m}Tc]HM-PAO was started after the patients were placed in the examination table. And [^{99m}Tc]HM-PAO injection was performed as soon as the preparation had been accomplished. Dynamic SPECT started immediately after i.v. injection of 3 mCi of [^{123}I]IMP or 20–30 mCi of [^{99m}Tc]HM-PAO. Prior to injection of [^{123}I]IMP the patients had been given iodine solution to block the thyroid. There was at least 2 days interval between these two SPECT studies.

TABLE 1
The Clinical Data of the Seven Patients in This Study

Case no.	Age	Sex	Histologic type	Angio-grade	L/N ratio (IMP)	L/N ratio (HM-PAO)	TAC (IMP)	TAC (HMP-PAO)
1	50	M	Angioblastic	I	452%	368%	Type I	Type I
2	60	F	Angioblastic	I	362%	164%	Type I	Type II
3	86	M	Unknown	II	255%	191%	Type II	Type II
4	59	M	Meningothelial	II	170%	146%	Type II	Type II
5	77	M	Transitional	II	169%	144%	Type II	Type II
6	42	F	Fibroblastic	IV	95%	96%	Type III	Type III
7	42	F	Fibroblastic	IV	74%	76%	Type III	Type III

Data Acquisition and Analysis

The detail of the SPECT technique was described in the previous report (*21*). In brief, this study was performed with a ring-type gamma camera (SET 020, Shimazu Co., Kyoto, Japan) and a hypersensitive collimator. The data acquisition was performed every 2 min for 20 min immediately after the injection of the tracers and ten serial images were obtained. The approximate number of counts of the [^{123}I]IMP SPECT were ~50,000–60,000 and 200,000–300,000 counts in the first and tenth images respectively, while those of [^{99m}Tc]HM-PAO SPECT were ~three- to fourfold higher than those of [^{123}I] IMP SPECT in the first images because of higher energy of ^{99m}Tc. Data analysis was done without smoothing.

Time-activity curves (TACs) were constructed and the counting-rate ratio for the lesion to the contralateral homologous presumed normal area (Lesion/Normal ratio, L/N ratio) was calculated in the first image. The vascularity of the tumor was graded to four grades by angiographic findings according to the method described in the previous report (*21*). Namely, extremely hypervascular meningiomas graded to Grade I and hypovascular ones to Grade IV. L/N ratios of these two SPECT studies were compared with angiographic grades.

RESULTS

The clinical data of the seven patients in this study were summarized in Table 1.

Time-Activity Curves

The pattern of [^{123}I]IMP uptake in the normal brain tissue was gradual increase, whereas that of [^{99m}Tc]HM-PAO was rapid saturation and subsequent stable reten-

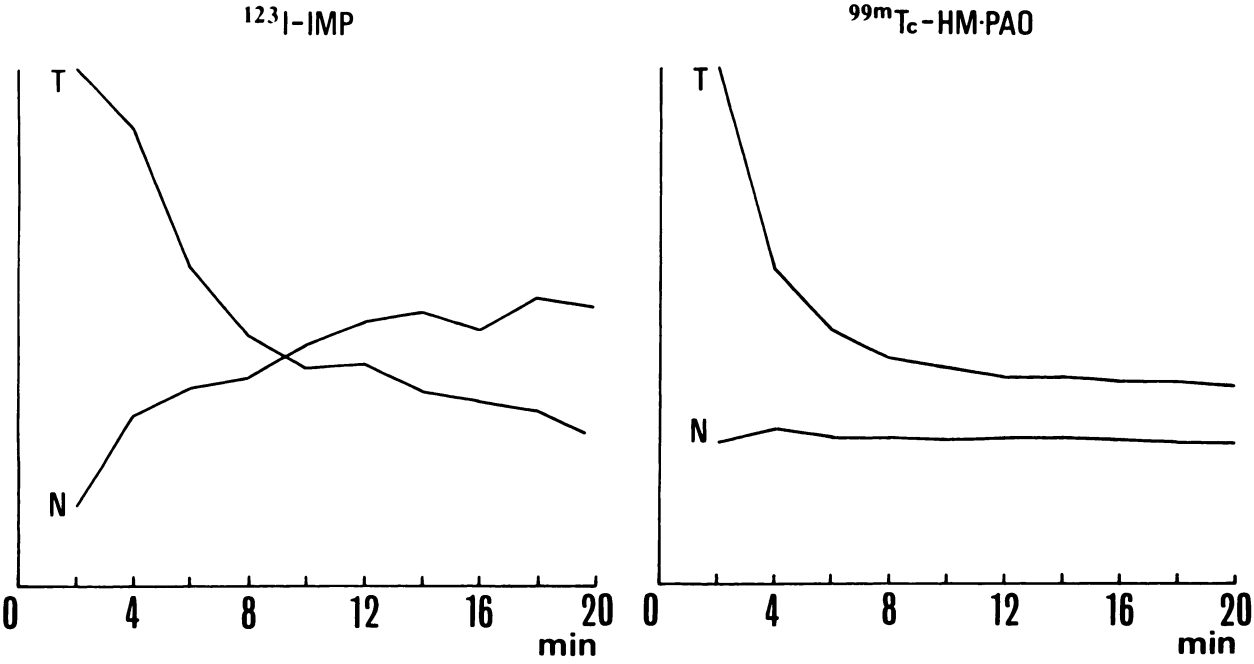

FIGURE 1
TAC of type I (Case 1). Left: TAC of [^{123}I]IMP SPECT; Right: TAC of [^{99m}Tc]HM-PAO SPECT. In this case the initial uptake of these tracers in the tumor was extremely high and L/N ratios of [^{123}I]IMP and [^{99m}Tc]HM-PAO SPECTs were 452% and 368%, respectively. Iodine-123 IMP in the tumor was washed out under normal level within 20 min, whereas the washout of [^{99m}Tc]HM-PAO in it was incomplete. The unit of the ordinate is number of counts in the ROI.

tion. TACs derived from the [^{99m}Tc]HM-PAO dynamic SPECT were classified into three types as those from the [^{123}I]IMP SPECT. Namely, type I is an initial high uptake and rapid washout type, type II is an initial high uptake and slow washout one and type III was an initial low uptake one. Of these seven meningiomas only one tumor (Case 1) showed TAC of type I. Even in the TAC of type I the curve of the radioactivity in the tumor had a very long tail at a higher level than normal brain tissue (Fig. 1). While, in an angioblastic meningioma (Case 2) the TAC of [^{123}I]IMP SPECT belonged to type I, whereas that of [^{99m}Tc]HM-PAO SPECT did to type II (Fig. 2). Another three meningiomas with TACs of type II in [^{123}I]IMP SPECT also showed TACs of type II in [^{99m}Tc]HM-PAO SPECT. They seemed to have some retention mechanisms of these two tracers. The other two fibroblastic meningiomas showed TACs of type III in both [^{123}I]IMP and [^{99m}Tc]HM-PAO SPECT studies (Fig. 3).

L/N Ratio

L/N ratios of the [^{99m}Tc]HM-PAO SPECT were lower than those of the [^{123}I]IMP SPECT, particularly in hypervascular meningiomas. In an angioblastic meningioma (Case 1) the L/N ratio of the [^{123}I]IMP SPECT was 452%, whereas that of the [^{99m}Tc]HM-PAO SPECT was 368%. In another angioblastic one (Case 2) the former was 362%, whereas the latter was only 164%. L/N ratios of another three meningiomas with angiographic Grade II were also slightly lower in the [^{99m}Tc]HM-PAO SPECT than in the [^{123}I]IMP SPECT. On the other hand L/N ratios of these two SPECT studies were very close in two fibroblastic meningiomas (Table 1).

DISCUSSION

For clinical rCBF measurement one can consider the use of a "chemical microsphere", i.e., a compound that is distributed in correlation to rCBF and is completely retained in the brain without having to revert to capillary blockade. The main requirements of "chemical microsphere" are high blood-brain barrier (BBB) permeability and retention of a fixed regional distribution for a period sufficient to permit image acquisition. Iodine-123 IMP has high BBB permeability and is extracted almost completely during a single passage through cerebral circulation in normal brain tissue. And it has been generally accepted that brain uptake of [^{123}I]IMP is a result of an affinity for nonspecific high capacity binding sites for amines (*1,2*). Though the initial distribution of [^{123}I]IMP in brain tissue reflects rCBF very well, its distributional pattern changes as time goes on (*6*). Time-activity curves in our study also showed gradual increase of [^{123}I]IMP uptake in brain tissue. Therefore, it is generally recognized that [^{123}I]

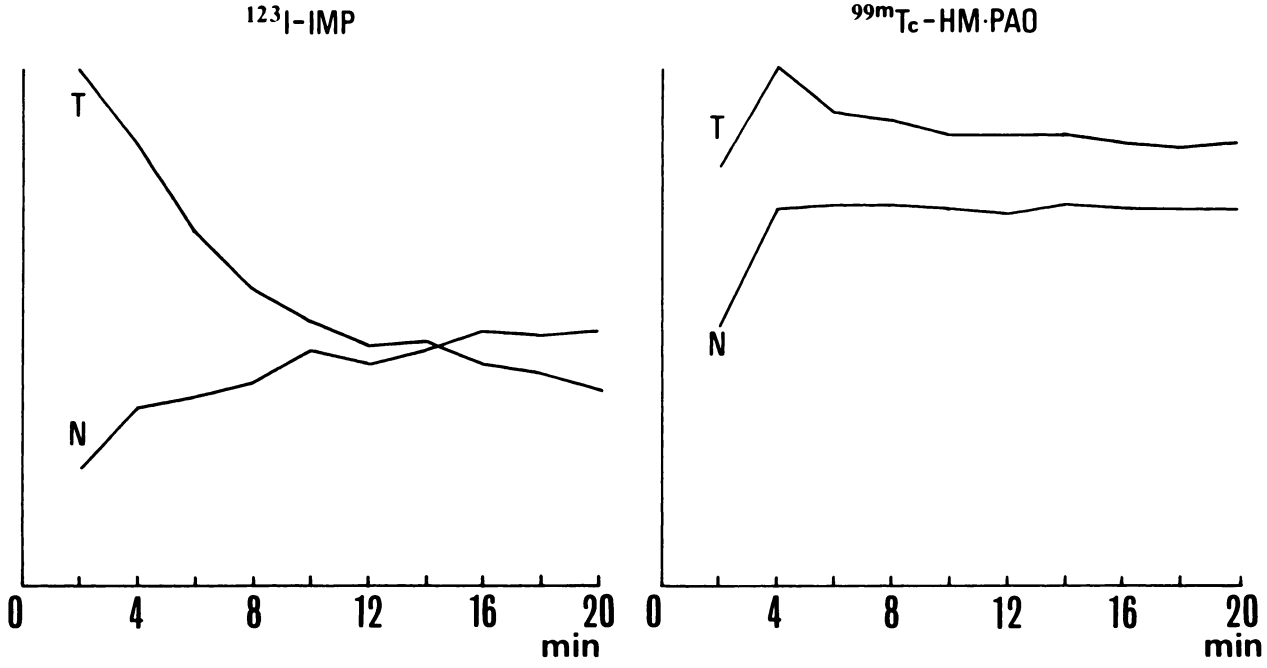

FIGURE 2
TAC of type II (Case 2). Left: TAC of [^{123}I]IMP SPECT; Right: TAC of [^{99m}Tc]HM-PAO SPECT. In this case the initial uptake of [^{123}I]IMP in the tumor was extremely high and L/N ratio was 362%. While, L/N ratio of [^{99m}Tc]HM-PAO SPECT was only 164%. Though [^{123}I]IMP in the tumor was washed out under normal level within 20 min, the washout of [^{99m}Tc]HM-PAO in it was quite slow and TAC showed continuous higher level of the radioactivity in it than in normal brain tissue.

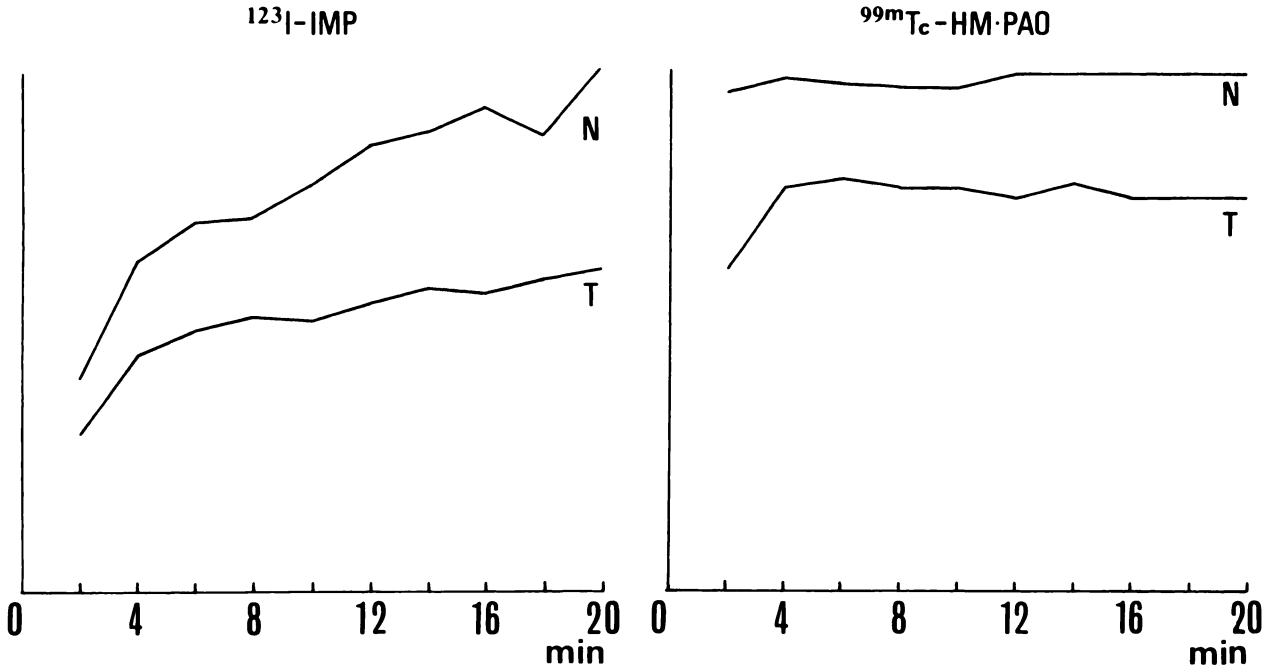

FIGURE 3
TAC of type III (Case 7). Left: TAC of [^{123}I]IMP SPECT; Right: TAC of [^{99m}Tc]HM-PAO SPECT. In this case the initial uptake of these tracers in the tumor was lower than in the normal brain tissue.

IMP is not a pure rCBF tracer. On the other hand, according to the report by Bok et al. (*22*), the brain uptake of [^{99m}Tc]HM-PAO reaches the plateau 5 to 10 min after i.v. injection and remained constant for the following several hours. TACs in our study also showed rapid saturation within 4 min and subsequent stable retention of [^{99m}Tc]HM-PAO uptake in brain tissue. Furthermore, because of shorter half-life of ^{99m}Tc, the radiation dose of [^{99m}Tc]HM-PAO to the patients should be lower even when higher activity doses are administered. Application of higher doses may result in higher quality images for clinical purpose. These properties of [^{99m}Tc]HM-PAO seemed to be ideal for routine rCBF imaging with SPECT. However, some drawbacks of [^{99m}Tc]HM-PAO have been noticed. First the partition coefficient of [^{99m}Tc]HM-PAO is only 0.42 ml and the initial brain extraction is no more than 40% (*23*). This may result in the lower L/N ratios of [^{99m}Tc]HM-PAO SPECT than those of [^{123}I]IMP SPECT in hypervascular meningiomas. L/N ratios of [^{123}I]IMP SPECT reflected the vascularities of meningiomas very well, whereas those of [^{99m}Tc]HM-PAO SPECT could not reflect them, particularly in hypervascular ones.

Second, the blood clearance of [^{99m}Tc]HM-PAO is quite slow and ~10% of injected activity still remains in blood after 30 min (*15*). Therefore, in extremely hypervascular meningiomas such as Case 1 intravascular radioactivity would remain for a long time even if the washout of the tracer in the tumor tissue had been completed. This may result in the long-term higher radioactivity in the tumor in Case 1.

In the [^{99m}Tc]HM-PAO SPECT all hypervascular meningiomas except for two fibroblastic meningiomas showed continuous higher radioactivity for 20 min in the tumor than in the normal brain tissue. This fact suggested some retention mechanisms of [^{99m}Tc]HM-PAO in meningiomas. Of course it is well known that free ^{99m}Tc accumulates in meningiomas. However, the radiochemical purity (RCP) of [^{99m}Tc]HM-PAO checked by thin layer chromatography (TLC) was reported to be higher than 90% immediately after the preparation (*16*). Though the RCP of injected [^{99m}Tc]HM-PAO was not examined, RCP was supposed to be more than 90% because it was injected immediately after the preparation. Therefore, accumulation of free ^{99m}Tc only cannot explain the long-term higher radioactivity in meningiomas. The trapping mechanism of [^{99m}Tc]HM-PAO in brain tissue is thought to be caused by conversion to a hydrophilic complex, possibly by opening of the bond between the oxime groups. After passage of the lipophilic [^{99m}Tc]HM-PAO through BBB the hydrophilic product is trapped inside the brain tissue. This conversion is accelerated by certain proteins (*24*). Meningiomas may have also this trapping mechanism of [^{99m}Tc]HM-PAO.

Many trials to demonstrate rCBF in brain tumors have failed because of the lack of retention mechanism of these tracers in their tissue, whereas [^{123}I]IMP dynamic SPECT has been demonstrated to be very useful to evaluate the vascularities of meningiomas (*21*). L/N ratio in the [^{123}I]IMP SPECT is an especially useful parameter of vascularity comparable to angiography.

On the contrary, [^{99m}Tc]HM-PAO dynamic SPECT could not reflect the vascularities of meningiomas, particularly in hypervascular ones.

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