PRELIMINARY NOTES

Decreased Accumulation of Isopropyl-Iodoamphetamine (I-123) in Brain Tumors

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Four out of four patients with brain tumors were observed to have impaired N-isopropyl-p-[^{123}I]iodoamphetamine (IAMPH) accumulation by the lesions even though brain scans with technetium-99m diethylenetriamine pentaacetic acid were normal in two. IAMPH may be a more sensitive means of detecting regional cerebral disease than tracers primarily sensitive to blood-flow abnormalities or impairment of the blood-brain barrier.

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Most clinical radionuclide studies of the brain assess the integrity of the blood-brain barrier. Lesions are detected as increased regional accumulations of tracers, such as technetium-99m in pertechnetate or diethylenetriamine pentaacetic acid (DTPA) (*1*). Substrates such as the glucose analog 2-[^{18}F]fluoro-2-deoxyglucose assess the glucose metabolic activity of the brain (*2,3*). In 1980, Winchell, Baldwin, and Lin (*4*) introduced a new compound, S(+)-N-isopropyl-p-[^{123}I]iodoamphetamine. They attributed the observed high initial uptake of this agent to its lipophilicity, and postulated that the uptake might also be a function of perfusion, pH gradients, or affinity for high-capacity, relatively nonspecific binding sites for amines.

We have studied four patients with biopsy-proven brain tumors. The lesions were characterized by a striking diminution of N-isopropyl-p-[^{123}I]iodoamphetamine accumulation despite the fact that all of them had normal or increased blood flow.

MATERIALS AND METHODS

After approval of research protocols by our Institutional Committee on Clinical Investigation, four patients were selected on the basis of a strong history and physical examination findings of brain tumor, abnormal transmission computerized tomography (TCT), cerebral angiographic findings preoperatively (patients M.L. and A.C.), or brain biopsy. Written informed consent was obtained for all cases. Three patients had Tc-99m DTPA brain scans and radionuclide angiography (*5,6*). Six to 9 mCi of S(+)-N-isopropyl-p-[^{123}I]iodoamphetamine* (IAMPH) was administered intravenously and imaging was begun at 10 min. This timing was selected because time-activity curves for monkey brain (*7*) revealed that iodoamphetamine activity leveled off within that time. The specific activity of the iodoamphetamine was 11.6 mCi I-123/mg IAMPH.

IAMPH images were obtained with a standard large-field-of-view (LFOV) scintillation camera, using a medium-energy, parallel-hole collimator and 1.6 magnification. Anterior, posterior, right and left lateral, and vertex views were acquired. Each image contained 400,000 counts and required 1.5 min. A 20% pulse-height window was centered around the 159-keV photopeak of I-123. In one patient, M.L., the radioactivity in tumor tissue obtained about 20 hr after IAMPH administration was measured in a well counter with a 20% pulse-height window centered at 159 keV.

Patient No. 1. M.L. was a 58-yr-old right-handed black female admitted April 1981 for the evaluation of sudden onset of left hemiparesis 10 days before admission. She had a history of hypertension, angina, and al-

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cohol abuse but no previous neurological problems. She had a mild left hemiparesis, decreased pin and temperature sensation on the left side of her body, somewhat brisker deep tendon reflexes on the left, and a left positive Babinski.

A TCT scan showed a ring enhancing area in the right frontal lobe surrounded by minimal edema and with moderate mass effect. A pertechnetate (Tc-99m) brain scan was not performed.

A large hypervascular lesion in the right frontoparietal area was seen at angiography, and a subtotal resection of this area was performed. Biopsy specimens revealed a Grade IV astrocytoma. The isopropyl iodoamphetamine study will be described under RESULTS.

Patient No. 2. A 34-yr-old right-handed white male (W.D.) was admitted for intra-arterial chemotherapy. He had previously been admitted for syncope, at which time a subtotal removal of a Grade III astrocytoma was accomplished followed by postoperative radiation. He subsequently developed progression of his headaches. A TCT scan revealed evidence of tumor recurrence: the same mass in the right thalamic and parietal areas with subfalcial herniation on the left. He received intra-arterial bischlorethyl nitrosourea (BCNU) without major complications. Tc-99m DTPA brain scan was abnormal.

Patient No. 3. C.M. was a 55-yr-old white male who originally presented with a left hemiparesis. He was found to have a right-sided frontoparietal Grade I astrocytoma that was treated with postoperative radiation therapy. He was readmitted for an episode of left-sided focal status epilepticus. TCT scan revealed a right frontal lucency with an enhancing area near the right ventricle and a 1 cm right-to-left shift, which was less than the shift on his original admission scan. Tc-99m DTPA brain and radionuclide angiography were completely normal. An EEG showed right frontotemporal slowing with some right central periodic sharp activity. The focal status responded well to increase of the patient's anticonvulsants.

Patient No. 4. A.C. was a 67-yr-old right-handed white female admitted for the evaluation of progressive left-sided weakness of several months' duration manifested by increasingly frequent episodes of falling and urinary incontinence. She had been in good health until 14 yr ago when she developed grand-mal seizures, which were completely controlled with anticonvulsant therapy.

The general physical examination on admission was normal. She was lethargic but oriented as to person, place, and time. She had slightly impaired memory, and diminished ability to perform arithmetic computations. She had impaired graphesthesia and two-point discrimination on the left side. There was mild weakness on the left side although her reflexes were symmetrical, and Babinski responses were absent bilaterally. Her gait was consistent with a mild left hemiparesis.

An EEG revealed recurrent runs of delta activity in the right temporal lobe without evidence of seizure discharges. A TCT scan showed a large, irregular lesion in the right hemisphere with decreased density, slight contrast enhancement surrounding the lesion, surrounding edema, and shift of midline structures. A right internal carotid angiogram demonstrated shift of the anterior cerebral vessels consistent with a mass in the right hemisphere and fine vascularity within the lesion. Tc-99m DTPA and radionuclide angiograms were normal.

The clinical impression was of glioma. At surgery a tumor was partially resected; microscopically it was a Grade III astrocytoma.

RESULTS

All four patients had strikingly decreased iodoamphetamine accumulation in the area of their brain tumors. Figure 1 shows three planar IAMPH views and a corresponding anterior Tc-99m DTPA view from one patient (A.C.). The tumor tissue from M.L., counted in a well counter, had no significant increase in activity over background levels. Of three patients in whom a Tc-99m DTPA brain study was performed, two studies were normal. In view of the contrast TCT scans in the patients, we cannot explain the two normal Tc-99m DTPA brain studies. However, the patients were selected in part be-

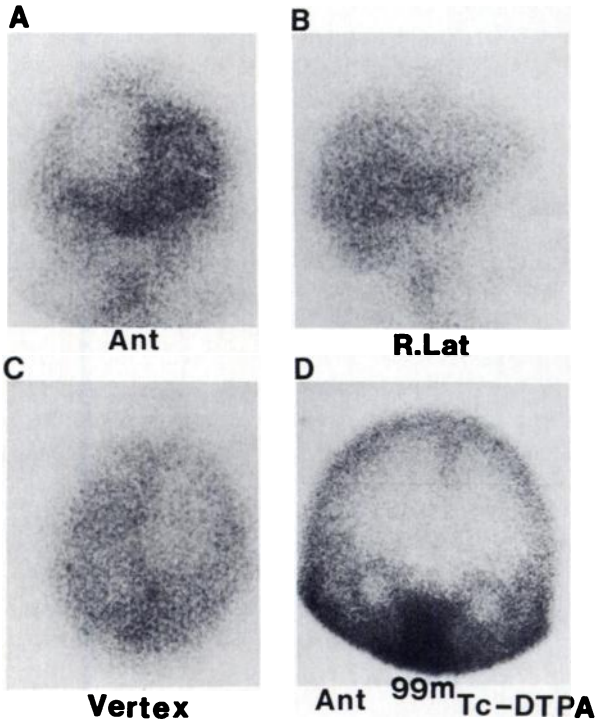

FIG. 1. (A) Anterior, (B) right lateral, and (C) vertex isopropyl-[I-123]iodoamphetamine images; (D) anterior Tc-99m DTPA image of patient (A.C.) with a Grade III astrocytoma.

TABLE 1. PATIENT DATA

Patient	Age/Sex	Histology	Vascularity*	Necrosis†
M.L.	57/F	Astrocytoma IV	Hyper-	None
W.D.	34/M	Astrocytoma III	Hyper-	None
C.M.	67/M	Astrocytoma I	Normal	None
A.C.	67/F	Astrocytoma III	Normal	None

* Assessed by angiography and/or Tc-DTPA radioangiography.
† Assessed by histology.

cause of abnormal TCT scans. Table 1 summarizes the data from the four patients.

DISCUSSION

Tracers such as technetium 99m in pertechnetate or diethylenetriamine pentaacetic acid (DTPA) have low lipid:plasma partition coefficients and are excluded from the brain by the blood-brain barrier. The mechanism of uptake of S(+)-N-isopropyl-p-[^{123}I]iodoamphetamine is incompletely understood. Accumulation, broadly speaking, is a product of blood flow and extraction efficiency. Pertechnetate is an example of a tracer with a low extraction efficiency in the normal brain, while IAMPH is an example of a tracer with high extraction efficiency in the brain (*8*). The initial uptake of IAMPH is in part a consequence of its lipophilicity, while retention is the result of some binding mechanism (*4*). Work by Winchell and others (*7*) revealed a first-pass extraction efficiency close to 100%. In studies of synaptosomes in dog and monkey they also found that norepinephrine uptake—and especially that of serotonin—were inhibited by IAMPH, and both serotonin and dopamine were released or displaced by this same agent. These findings suggested that IAMPH may be bound by amine binding sites. Reports by Kuhl et al. (*8*) have shown that in normal animals, IAMPH uptake correlates well with regional cerebral blood flow as measured by microspheres, and that tomographic images in patients resembled those of ammonia (N-13) and fluorodeoxyglucose(F-18) obtained by positron ECT.

Our findings of impaired tracer uptake in brain tumor suggest that the tracer may represent an important new agent for the study of the brain. The lower activity seen in these lesions could represent reduced blood flow or a lack of binding sites, permitting more rapid washout. In view of the normal or increased vascularity of the lesions at angiography and the lack of necrosis at biopsy of all four lesions, the latter is the more likely mechanism. This suggests that impaired extraction efficiency of this tracer and retention by brain may be sensitive to the presence of disease.

FOOTNOTES

We have now studied a total of 11 patients with biopsy proven primary brain tumor. All eleven have shown diminished IAMPH accumulation in the area of the brain tumor.

* Medi-Physics, Inc.

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