Cerebral Dynamics of *N*-Isopropyl-(^{123}I)*p*-Iodoamphetamine

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Temporal changes in the distribution of *N*-isopropyl-(^{123}I)*p*-iodoamphetamine (IMP) within the brain are measured with serial tomographic imaging. In the cerebellum there is a decrease in activity of 42% from the early [15–45 min postinjection (p.i.)] to the late (210–240 min p.i.) scan, while in the cortex the decrease is 18%, and in the basal ganglia there is no decrease within this time. In brain tumors there was no IMP uptake in the early as well as in the late scans, regardless of tumor type, perfusion rate, or blood-brain barrier dysfunction. In 11 of 43 patients with a cerebral infarction a real increase of ^{123}I activity (mean +21%) was seen in the late images. This "filling in" phenomena might be useful in selecting patients for bypass surgery. In these patients the diaschisis cerebelli, seen in the early scans, disappeared in the late images. The regional distribution of IMP changes with time; spatial ratios might be blurred by temporal changes. High-flow areas such as visio-auditory centers can be delineated clearly after stimulation in fast early scans; in these areas the pharmacokinetics of ^{123}I are different from other cortex regions. To get the full information from the IMP brain uptake, both spatial and temporal variation must be measured.

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The mechanism of *N*-isopropyl-(^{123}I)*p*-iodoamphetamine (IMP) brain uptake has been discussed in detail (*1–5*), but what the mechanism of uptake and retention is has not been clearly shown. The initial regional distribution might be flow and receptor dependent, followed by a "steady state" of 1–2 hr as an essential for single photon emission computed tomography (SPECT) with a rotating gamma camera system. Autoradiographic studies demonstrated dynamics in regional distribution thereafter (*3,6*), but little is known about dynamics in human brain areas. If there would be a difference in regional pharmacokinetics, SPECT by rotating gamma cameras might be of limited value; temporal variation might blur spatial distribution. A differentiation of brain tumors would be possible if a tumor-type dependent kinetic could be established. Looking for different pharmacokinetics in normal, hyper-, and hypoperfused brain areas and primary brain tumors, we began a prospective study.

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MATERIALS AND METHODS

Patient Selection

A total of 113 patients was investigated in a prospective study within a protocol approved by our institution's ethics committee and after informed consent had been obtained. In 23 patients a differentiated thyroid carcinoma had been treated with surgery and iodine-131 (^{131}I) ablation (age 18–43 yr). In no patient was there evidence of metastasis or neurologic dysfunction; for the purpose of this study they are called "normals." In another 47 patients a primary brain tumor was ascertained from other investigations (computed tomography (CT) with contrast enhancement, angiography) and confirmed after the SPECT by histology (age 19–38 yr). In 23 cases the diagnosis was meningioma, in another nine astrocytoma grade I/II and in 15 glioblastoma grade III/IV. These patients are called "tumor group." As a third group, 43 patients (age 16–62 yr) with an occlusion of one middle cerebral artery were studied 2–4 wk after stroke or trauma and before bypass surgery. In these patients the other vessels were normal as confirmed by angiography.

Patient Preparation

The iodine-123 (^{123}I) was produced by the (p,5n)

reaction 12–24 hr before injection. The IMP was synthesized by a rapid exchange method (*7*) by one of us (P.G.) within 45 min. There was no contaminant of ^{124}I, and that of ^{125}I was <1% at the time of injection. The radiochemical purity as assessed with thin layer chromatography and autoradiography was >97%, the specific activity of IMP >0.5 Ci/mmol.

To stimulate the audiovisual centers, the patient was placed on the SPECT table in a well-lit room and spoke with the physician (H.C.,O.S.), while 0.1 mCi/kg body weight were injected as a bolus through an i.v. line. With a special head holder the patient's head was positioned with the orbitomeatal line perpendicular to the collimator's surface and then fixed. For later studies, the patient was placed in the head holder exactly as before to get comparable slices.

Data Acquisition and Analysis

A commercial single-head SPECT system† fitted with a low-energy, high-resolution collimator was used. Inhomogenity was controlled by special hardware equipped to the camera. The photopeak was set at 160 keV with a 20% window. Data acquisition was done in 64 projections into a 128 × 128 byte matrix.‡ Acquisition time was set to 20 sec per projection resulting in a total time of 29.2 min for the SPECT study. The brain uptake of IMP was measured by planar imaging in both the anterior and posterior views before the first SPECT study and compared with those of phantom studies. The spherical phantom had a diameter of 20 cm and was filled with known amounts of ^{123}I solutions. The brain uptake as calculated from both views was between 7.2% and 8.7% of the injected dose, the total number of counts per SPECT study between 2.5–3.4 million.

In "normals" three studies were done: from 15 to 45 min, 1 to 1½, and 3½ to 4 hr p.i. In the other groups only an "early" (15–45 min) and a "late" (3½–4 hr) study was done.

For the reconstruction of transversal, sagittal, and coronal slices commercial software with filtered back projection and a low resolution Hanning filter were used without attenuation or scatter correction. The in-slice resolution in the reconstructed image was estimated from phantom studies (line source) with 1.6 cm FWHM. This is better than the FWHM of a LEAP collimator in another ^{123}I study with a rotating gamma camera (2 cm) (*8*), and in the same range as the FWHM of a multidetector brain scanner (1.7 cm) (*9*).

TABLE 1
Reproducibility of Head SPECT Uptake Measurements with ROI Technique (15 Normals with MDP SPECT 2 and 3 hr p.i., Early Left-to-Right Ratio 1.0, Mean ± 1 s.d.)

Temporo-mandibular joint	1,02 ± 0,03
Orbital region	0,99 ± 0,02
Occipital region	1,02 ± 0,02

Data analysis was done without further data manipulation (i.e., smoothing, interpolation, etc.). Slices with a depth of 4 pixels (1.2 cm) were reconstructed from the lower edge of the cerebellum up to the top of the cortex from the early, middle, and late studies. Regions of interest (ROIs) of at least 11 pixels length and width (twice the spatial resolution of the reconstructed image) were drawn for each slice around the frontal, right and left lateral, and occipital cortex as done by von Schulthess (*8*), carefully excluding stimulated high-flow centers, right and left cerebellum, and the area of right and left basal ganglia. "Tumor" and "infarction" regions were delineated separately by manual outlining of ROIs and the mean count rate per voxel estimated in each ROI. With this technique, total volume of "tumor" or "infarction" as well as that of normal structures could be counted and compared in the different studies. Smaller variations in positioning will not disturb the comparison of different scans in the same patients as might be with the single-slice technique.

To estimate the reproducibility of this technique, 15 patients with normal bone scan were studied in the same manner 2 and 3 hr after application of 20 mCi [^{99m}Tc]MDP. The right-to-left ratio of temporo-mandibular joints, an orbital and an occipital region were calculated using nine voxels each. The reproducibility of uptake measurement with our technique of head fixation and ROI setting is within acceptable limits (Table 1).

The lung uptake of IMP was recorded within another protocol both immediately before each SPECT study by planar imaging and continuously by a single probe technique (*10*). The probes were carefully placed over the heart and lateral parts of both lungs. The uptake was measured for 4 hr and then corrected for the intravascular component. The corrected curve represents the washout of IMP from the lung parenchyma only (*10*).

The significance of differences was calculated using the paired u-test.

RESULTS

Kinetics in Normals

In the lungs, there was a decrease of 50% from the early to the late images (Table 2). The downslope of the time-activity curve as measured with single probes could be fitted best by a monoexponential function with a half-life time of 205 ± 18 min. In the normal cortex the mean difference between the early and the late scan is significant, while the decrease of 8% in the 1-hr scan is not significantly different from both other values (Table 2). In the cerebellum the decrease is 44% for the late and 19% for the 1-hr scan. In the basal ganglia there were no significant differences in the uptake.

Stimulated visio-auditory centers could be delineat-

TABLE 2
Changes in Relative Uptake of IMP (Early Scan = 1.0, Arithmetic Mean and 95% Range)*

Scan	90–120 (min)	210–240 (min)
Lung	0.76 (0.68–0.87)†	0.50 (0.42–0.63)†
Cortex	0.92 (0.81–1.03)	0.81 (0.72–0.93)‡
Cerebellum	0.81 (0.63–0.96)‡	0.56 (0.43–0.76)†
Basal ganglia	0.97 (0.89–1.06)	0.95 (0.88–1.04)
"Ischemia"	—	1.21 (1.10–1.36)‡

* Difference to early scan significant with † = ($p < 0.01$), ‡ = ($p < 0.05$).

ed in 61% of all early studies (Fig. 1). In these patients the difference to the late scan was significant ($p < 0.05$) wth 28% for the occipital and 23% for the temporal region.

Kinetics in Pathologic Conditions

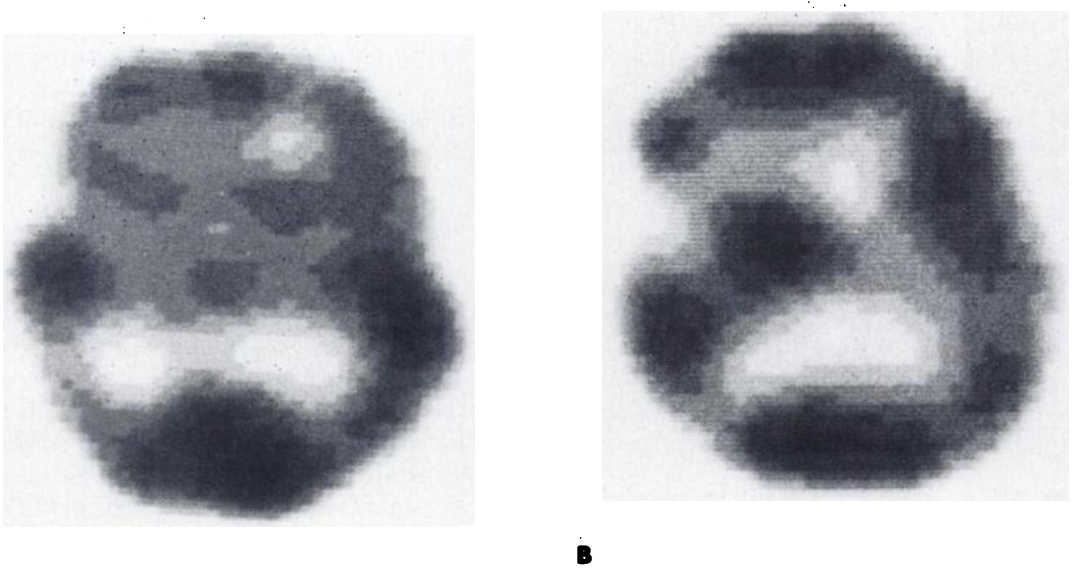
In brain tumors there was no IMP uptake in the early as well as in the late scan, regardless of tumor type, perfusion rate, or blood-brain barrier dysfunction (Fig. 2). Twenty-five tumors had a high-flow perfusion pattern in dynamic brain scanning, 41 had damage of the blood-brain barrier demonstrated both by conventional radionuclide scans and CT scans with contrast enhancement.

In the patients with occlusion of one mid-cerebral artery the counts per voxel in the reconstructed slices ranged from 38 to 80% of that of the contralateral side (Fig. 3). This may reflect both the limited spatial resolution in the reconstructed images and a retrograde perfusion. In 11 of these 43 patients, an increase was seen in the late images (Fig. 4). This significant increase in mean counts per voxel represents a true "filling in" of ^{123}I to this ischemic region, either as IMP or as some metabolites. In these patients the diaschisis cerebelli (ratio abnormal to normal cerebellum in the early scan 0.64, range 0.46–0.79) also disappeared with time (ratio in the late scan 0.83, range 0.68–0.94, $p < 0.05$).

DISCUSSION

The pharmacokinetics of IMP and its analogs have been studied extensively in experimental animals (*1,4,6*). There seems to be some difference in humans; for example, the high eye uptake of baboons is not seen in man (*4*). There are few kinetic data, however, available in man. The half-life of IMP lung clearance has been measured in one study as <30 min, while that of HIPDM was about 60 min (*5*). This differs from our figure for IMP of 205 min and from that of others for HIPDM in nonsmoking, healthy adults of 6.4 hr (*11*). The later two measurements were done with single probes placed at different sides of both lungs, carefully avoiding larger vessels in the field of view (*10*). Preferentially parenchymal uptake was measured, while in the other study (*5*), uptake in the whole upper lung fields was counted; therefore, preferentially intravascular kinetics of IMP and HIPDM were measured.

Another study compared regional cerebral blood flow estimated by the tomographic xenon-133 (^{133}Xe) washout technique with repeated IMP SPECT scans (13-27, 33-47 min and 5.5 hr p.i.) in 20 patients with unilateral cerebrovascular disease. Only in the initial



A B

FIGURE 1
A: Early (15–45 min) IMP scan in "normal" patient with stimulation of visio-auditory centers by light and language. Slice thickness is 1.2 cm. B: Late (210–240 min) scan in same patient

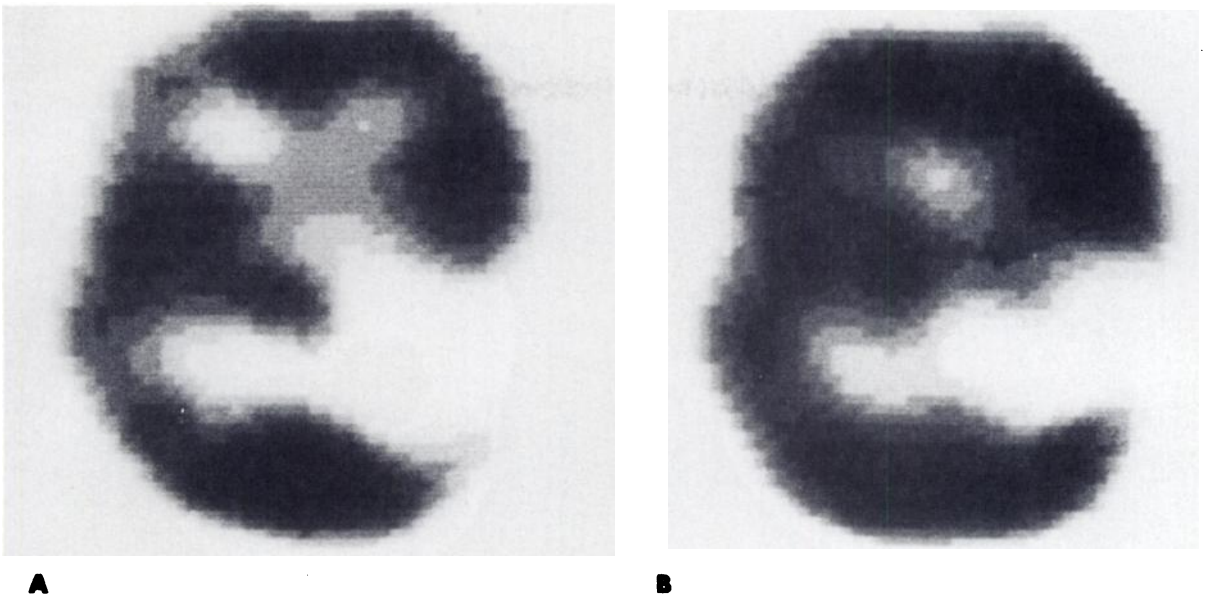


FIGURE 2
A: Early (15–45 min) IMP scan in patient with low-grade astrocytoma. Slice thickness is 1.2 cm. B: Late (210–245 min) scan in same patient

SPECT scan was the IMP hemispheric uptake ratio not significantly different from the ^{133}Xe ratio (*12*). Therefore, IMP SPECT images done later than 30 min p.i. (*9*) will no longer reflect regional cerebral blood flow. In late IMP SPECT scans of patients with coronary artery disease the "redistribution" or "filling in" phenomena was seen (*12*) as in some of our patients. These concordant findings might be explained by the "penumbra effect" (*13*): The infarcted area will be surrounded by a region of limited blood flow which will keep the cells alive but is insufficient to allow normal metabolism. The patient with "filling in" after stroke might be the ideal candidate for bypass surgery.

In our patients with infarction of one midcerebral artery (MCA) the measured uptake was between 38–80% of that of a corresponding contralateral region. These findings correspond well with those of another study using a high resolution instrument: In their patients with severe physical deficits after MCA infarction the uptake was between 20–80%, while in patients with minor deficits a near normal uptake was seen (*14*). The minor spatial resolution of the rotating gamma camera seems not to disturb the uptake measurement, at least in such large regions as the territory of the MCA; the high ^{123}I uptake in "infarcted" areas will probably reflect reperfusion or redistribution of metabolites. This too will be concludent with the finding of "filling in" in late scans in these areas.

Our results demonstrate that only serial imaging can extract both spatial ("regional blood flow") and temporal ("functional state") variation in the IMP uptake. Temporal variation is highest—as measured by our technique—in the cerbellum or stimulated cortical regions and lowest in basal ganglia. The delineation of activated temporal or occipital regions in the early scan was possible in two out of three studies using a high-resolution collimator.

Abnormal brain cells (primary tumors) lost the capability of IMP extraction regardless of blood flow or blood-brain barrier dysfunction. This has been demon-

FIGURE 3
Early (15–45 min) IMP scan in patient with post-traumatic occlusion of right cerebral artery without "filling in." Late image is identical

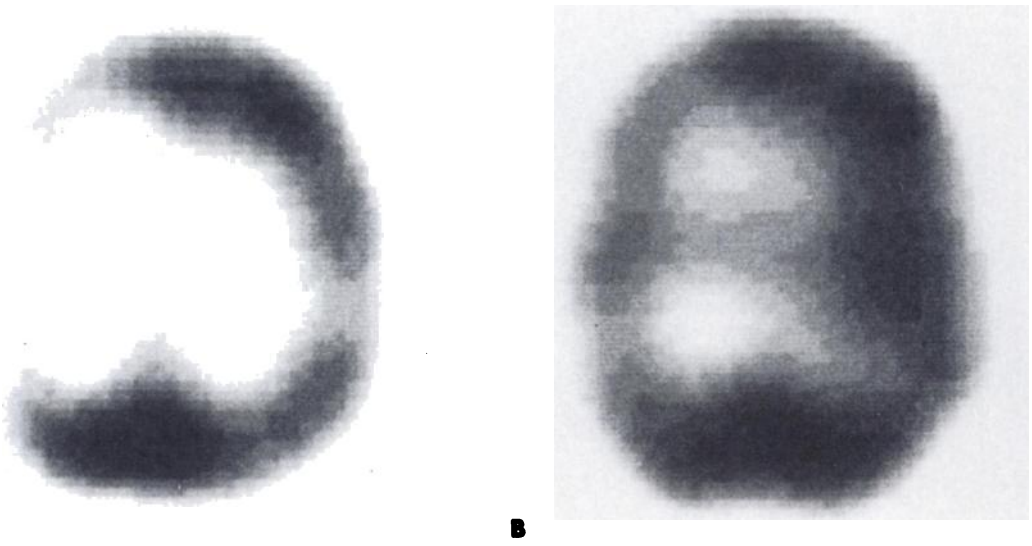


FIGURE 4
A: Early (15–45 min) IMP scan in patient with post-traumatic occlusion of left midcerebral artery. B: Late (210–240 min) IMP scan in same patient. In territory of occluded vessel there is not only relative, but also absolute increase in counts per voxel of 24% from early to late scan, a real "distribution"

strated in a study of four patients with planar imaging (*2*). The dynamic SPECT demonstrated that there is not only no initial uptake of IMP by rapid extraction, but also no late uptake, as seen in hypoperfused ischemic regions. This will strongly indicate the loss of specialized receptors for IMP-binding at the cell surface of these primary brain tumors. Dynamic IMP SPECT cannot add any information for differentiating primary brain tumors.

Serial IMP SPECT imaging enables not only a rough view into the physiology of brain function, but also measures the redistribution of activity within the territory of occluded arteries. Whether this "filling in" can predict the effect of bypass surgery is still under investigation; initial results are encouraging.

The image quality of our fast serial scans with the homemade IMP is comparable with those of earlier PET scans because of the absence of ^{124}I. The high specific activity and the low contamination of ^{125}I (<1%) allows the application of large quantities of IMP (0.1 mCi/kg body weight); nevertheless, IMP brain SPECT with a rotating gamma camera is inferior to PET imaging. What is needed is a much faster system with a higher spatial resolution (*15*) to determine the IMP pharmacokinetics in detail.

FOOTNOTES

† Siemens Medical Systems, Iselin, NJ (ZLC 370 with Orbiter).

‡ Medtronic/MDS, Ann Arbor, MI (A-3).

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