Temporal Changes in Accumulation of N-Isopropyl-*p*-Iodoamphetamine in Human Brain: Relation to Lung Clearance

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Temporal changes in brain uptake of ^{123}I-labeled N-isopropyl-*p*-iodoamphetamine (IMP) were studied by means of a multi-detector single photon emission computed tomography (SPECT) scanner. Serial dynamic SPECT scan was performed for 50 min following an i.v. bolus injection of IMP in 30 patients with various neurologic diseases. In 18 of them the radioactivity in the lung was also recorded by a single probe detector during the serial dynamic SPECT scan. Brain activity showed a gradual increase after the injection of IMP, reaching 63 ± 7% of the maximum activity at 5 min and 90 ± 5% at 20 min. The lung clearance showed a large variation among the individual cases; 29 to 72% (52 ± 11%) of the initial peak activity at 20 min and 22 to 57% (41 ± 9%) at 50 min after the injection. A significant positive correlation was observed between the clearance half-time in the lung and the time to reach 90% of the maximum activity in the brain ($r = 0.86$, $p < 0.001$). These results suggested that brain uptake of IMP is influenced by the lung clearance and the optimum time to start SPECT data acquisition using a conventional rotating gamma camera system is 20 min after the injection.

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Iodine-123- (^{123}I) labeled N-isopropyl-*p*-iodoamphetamine (IMP) has been used for mapping of brain perfusion with single photon emission computed tomography (SPECT) (*1,2*). This compound has high extraction and subsequent retention in the brain (*3*), which are ideal characteristics for brain perfusion SPECT imaging. On the other hand, as with various other amine derivatives, a considerable amount of lung uptake of IMP was reported both in animals and in human subjects (*4–6*). The increased trapping of IMP in the lung may cause a delayed delivery of the tracer to the brain.

SPECT methodology is based on the assumption of stable radioactivity distribution during data acquisition. However, a rotating gamma camera system widely used in most of the nuclear medicine facilities for SPECT imaging requires a fairly long acquisition time (usually 30 to 40 min with a single head camera) because of the low sensitivity and the mechanical rotation of the detector, and it may bring a significant error for the reconstruction of SPECT images. Therefore, it is important to show the kinetics of IMP in the brain for SPECT imaging.

In the previous report we have demonstrated the possible effect of the lung clearance of IMP on the brain activity (*6*). In order to examine the temporal changes of radioactivities in the brain and the lung, we performed serial dynamic SPECT imaging using a multi-detector SPECT scanner (*7*), which allows fast dynamic SPECT imaging, along with continuous monitoring of the radioactivity in the lung.

METHODS

Radiopharmaceutical

We used IMP (0.45 mg of N-isopropyl-*p*-iodoamphetamine hydrochloride in 3 ml saline solution) labeled with 3 mCi of ^{123}I obtained by (p,5n) reaction (Nihon MediPhysics, Takarazuka, Japan). The subjects received a bolus injection of IMP (3 mCi) via a cubital vein. Potassium iodide (30 mg/day) had been given to the patients to block the thyroid uptake of the free radioactive iodine.

Subjects

A total of 30 cases (16 males and 14 females, age 54.7 ± 15.4 yr) with various neurologic diseases were studied. These

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included ten cases with cerebrovascular disease, six cases with dementia, two cases with brain tumor, and 12 other cases with degenerative neurologic diseases, such as Parkinsonism and adrenoleukodystrophy. Medication was not ceased for the study, and no sedation was given to the patients. None of these cases had pulmonary diseases determined by subjective symptoms and chest x-ray films.

Data Acquisition

Serial dynamic SPECT scan was performed by means of a multidetector SPECT scanner (Shimadzu Corporation, Kyoto, Japan) (*7*). The scanner consisted of three detector rings at 30-mm intervals, which permitted simultaneous acquisition of three SPECT images. Each detector ring was equipped with a circular arrangement of 128 sodium iodide crystals (14 × 26 × 30 mm). The use of a high-resolution rotating collimator for brain imaging provided a spatial resolution of 11.0 mm in terms of a full width at half maximum (FWHM) in the transaxial plane and 23.5 mm in FWHM in the axial direction. The maximum field of view was 25 cm in diameter with this collimator. The sensitivity measured by a 20-cm diameter cylindrical phantom filled with uniform technetium-99m (^{99m}Tc) solution was 6.6 kcps/μCi/ml.

The subject was positioned in the gantry by aligning the bottom slice as 2 cm above the orbitomeatal (OM) line, so that a total of three slices corresponding to 2, 5, and 8 cm above the OM line were obtained. Serial dynamic SPECT scan was performed every 2.5 min for 50 min after the injection of IMP. In 18 of them, the temporal changes of radioactivity in the lung were measured by the single probe detector made of sodium iodide crystal provided in the SPECT scanner (*7*). The lung activity was monitored by placing the detector on the right chest wall and recorded as sum of the counts every 10 sec.

Data Acquisition

All SPECT images were reconstructed using a filtered back-projection algorithm with Shepp-Logan filter convoluted with Butterworth filter (cut-off frequency 0.3 and order 4) (*8*). The total counts in the brain were calculated in the middle slice of each SPECT image and expressed as percentage to the radioactivity at 50 min after the injection. No correction was made for the physical decay of the radioactivity. The significance of the correlation coefficient was examined by the Student's t considerations to test the null hypothesis (*9*).

RESULTS

Figure 1 shows an example of the serial SPECT images obtained every 2.5 min following the injection of IMP in a case with transient ischemic attack. A gradual increase in brain activity was noted after the injection. In the initial several SPECT images, relative decrease of IMP uptake was observed in the bilateral front-parietal and temporo-parietal regions. However, these defects disappeared in the later images. An x-ray transmission computed tomography (CT) scan did not show any abnormality in this case.

An example of the temporal changes of the brain and the lung activity is shown in Figure 2. From these time-activity curves in the lung and the brain, the following parameters were calculated: clearance half-time ($T_{1/2}$) in the lung, time to reach the maximum activity (peak time), 90% of the maximum activity ($T_{0.9}$), and 50% of the maximum activity ($T_{0.5}$) in the brain. Table 1 shows the summary of the parameters of lung clearance and brain uptake. Peak time in the brain varied from 35 min to 50 min and four cases showed an increase of the brain activity even at 50 min after the injection. The average value of the brain peak time was 45.2 ± 4.9 min (mean ± s.d.). The time to reach 90% ($T_{0.9}$) of the peak count in the brain was also scattered in a wide range (12.3 – 30.8 min) but the time to reach 50% ($T_{0.5}$) was observed within 5 min (2.0 – 4.7 min).

Figure 3 summarizes the temporal changes of the brain activity in the total 30 cases. The brain activity reached only 62.9 ± 7.2% of the maximum activity at 5 min and 75.8 ± 6.5% at 10 min after the injection. On the other hand, the values in the later period revealed less variation and the brain activity reached 89.6 ± 4.9% at 20 min and 96.1 ± 3.3% at 30 min.

The lung clearance showed a large variation among the subjects. For example, the lung activity at 5 min ranged from 46% to 83% of the maximum activity, 29% to 72% at 20 min, 27% to 67% at 30 min and 22% to 57% at 50 min. Figure 4 summarizes the temporal changes of the lung activity in the 18 cases. Following a rapid clearance after the injection of IMP, the activity showed a gradual washout from the lung, reaching 60.7 ± 10.7% at 20 min, 47.7 ± 9.9% at 30 min, and 40.7 ± 9.3% at 50 min after the injection.

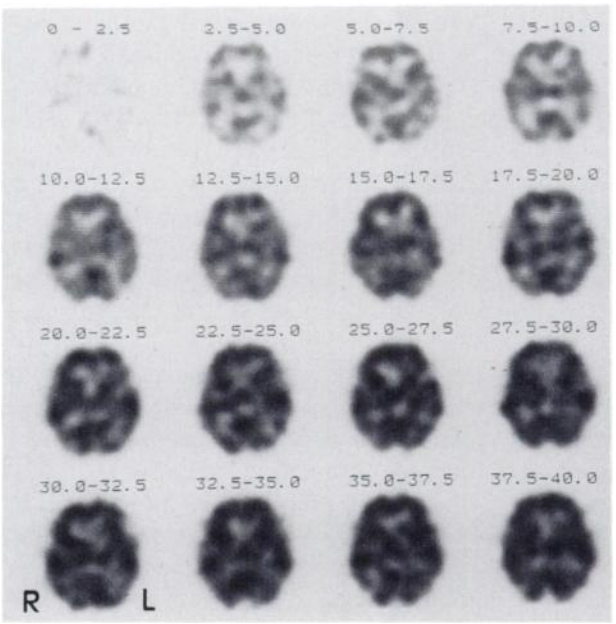

FIGURE 1
Serial brain SPECT images with IMP obtained every 2.5 min following IMP injection in a case with transient ischemic attack. Only 16 images until 40 min after the injection in the middle slice are shown.

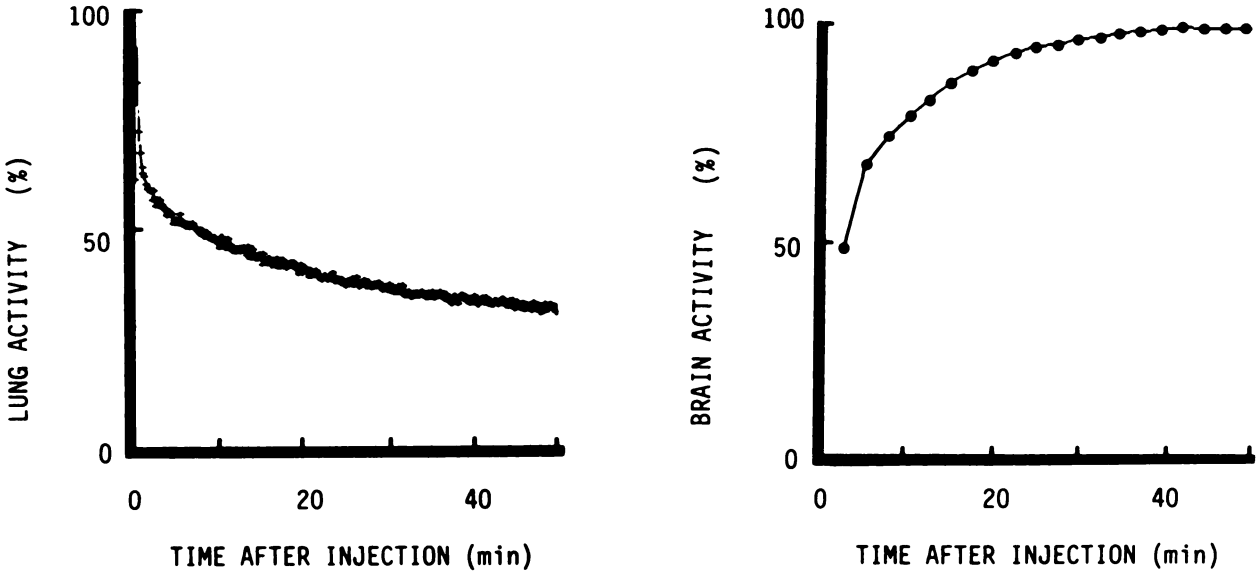

FIGURE 2
Example of temporal changes in activities in the lung and the brain.

Lung clearance $T_{1/2}$ varied from 3.7 min to over 50 min. In three cases, the activity in the lung was still greater than 50% of the maximum activity at 50 min after the injection and the lung clearance $T_{1/2}$ could not be calculated. The average value of $T_{1/2}$ except these three cases was 21.4 ± 13.5 min. Figures 5 and 6 show comparisons of the brain uptake and the lung clearance in 15 cases. A significant positive correlation was observed between lung clearance $T_{1/2}$ and brain uptake $T_{0.9}$ ($r = 0.86$, $p < 0.001$) as shown in Figure 5. However, a comparison between the lung clearance $T_{1/2}$ and the brain uptake $T_{0.5}$ showed a weak positive correlation ($r = 0.62$, $p < 0.05$).

DISCUSSION

Various new radiopharmaceuticals labeled with ^{123}I or ^{99m}Tc have been developed for brain perfusion SPECT. Among them IMP is one of the pioneering compounds and now available for clinical use in many countries. Although the clinical value of IMP has been established in various neurologic diseases, major disadvantages of IMP for brain perfusion SPECT imaging are relatively slow accumulation in the brain and requirement of long data acquisition time because of limited administration dose. Moreover, the activity is gradually washed out from the brain, and the IMP distribution in the later period does not reflect blood flow distribution any more (*6*). Therefore, the optimum time for SPECT data acquisition using the rotating gamma camera system is of great importance for the clinical studies.

The present study demonstrated a gradual increase in brain uptake of IMP, which was significantly correlated with lung clearance. The results indicated that the delivery of the tracer into the brain is strongly influenced by the washout from the lung. In spite of the

TABLE 1
Lung Clearance and Brain Uptake of IMP

	n	Range	Mean ± s.d.
Brain uptake			
peak time	30	35.0–50 min	45.2 ± 4.9 min
$T_{0.9}$	30	12.3–30.8 min	20.9 ± 5.1 min
$T_{0.5}$	30	2.0–4.7 min	3.4 ± 1.5 min
Lung clearance			
$T_{1/2}$	18	3.7–50 min	21.4 ± 13.5 min*

*Three cases which showed the lung activity >50% of peak count at 50 min after injection were not included.

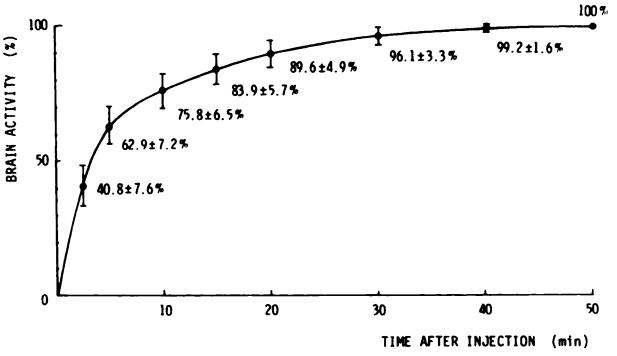

FIGURE 3
Summary of the temporal changes in brain uptake of IMP in 30 cases. Average values with s.d. are shown.

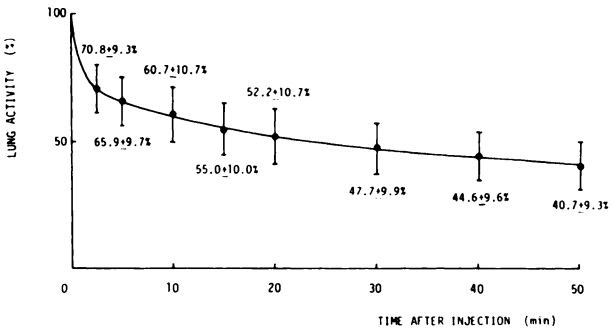

FIGURE 4
Summary of the temporal changes in lung clearance of IMP in 18 cases. Average values with s.d. are shown as percentage of the initial peak activity.

large variation for the lung clearance among the individual cases, however, the brain activity reached nearly 90% of the maximum activity at 20 min after the injection in most cases. The results obtained in this study suggested that SPECT data acquisition using the rotating gamma camera early after the injection may result in some artifacts for reconstruction of the images. The optimum time for data acquisition may be different in each case, but it would be safer if the scan could be performed for 15 to 20 min after the injection.

The temporal changes of the brain activity reflect the balance of the input and the washout of the tracer. The former is mainly determined by the arterial concentration of IMP and cerebral blood flow. Therefore, IMP SPECT images obtained early after the administration show an excellent correlation with regional cerebral blood flow except for some diseased cases with high blood flow, such as brain tumor and luxury perfusion

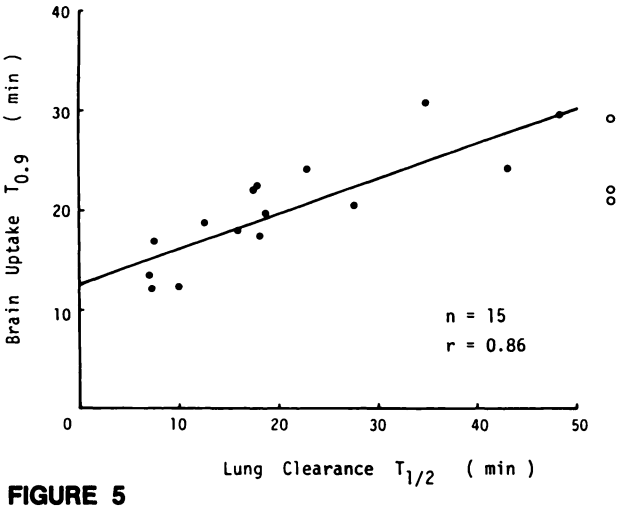

FIGURE 5
Comparison of time to reach 90% of the maximum activity in brain (Brain $T_{0.9}$) and clearance half-time in lung (Lung $T_{½}$). Three cases which showed the lung $T_{½} > 50$ min were not included in calculation (same for Fig. 6).

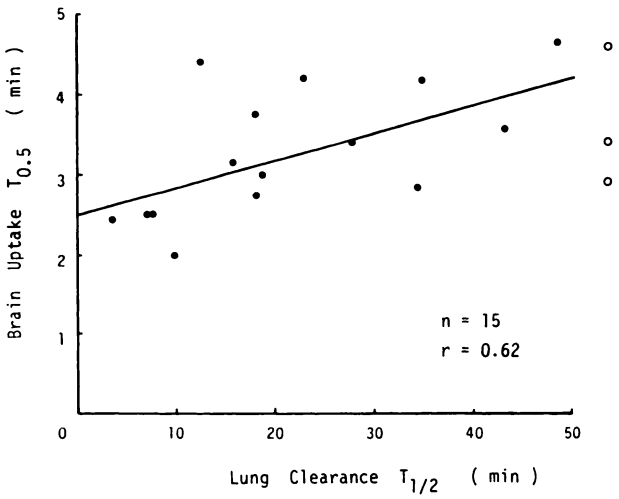

FIGURE 6
Comparison of time to reach 50% of the maximum activity in brain (Brain $T_{0.5}$) and clearance half-time in lung (Lung $T_{½}$).

(*6,10*). On the other hand, the latter is influenced not only by cerebral blood flow but also by other factors, such as retention mechanism and metabolism of the tracer (*3,11*).

In the previous study, we have demonstrated the different kinetics of IMP both among the normal brain structures and between the normal and diseased regions, suggesting the altered extraction and/or retention of IMP in these regions (*6*). The serial changes of the brain activity degraded the contrast of mild hypoperfused area in the later SPECT images obtained even within an hour after the administration (*6,12*). In this regard, the use of the conventional rotating gamma camera for brain perfusion SPECT with IMP may suffer from some limitations for detecting the mild ischemia. In addition, the delayed lung clearance may also affect the brain kinetics because it will give the continuous input of the tracer into the brain. This factor should be considered for the assessment of early and late SPECT imaging (so-called "redistribution" phenomenon) (*13*) or the washout analysis in the brain (*14*).

The reason for different clearance rates of IMP from the lung has not been elucidated. Previous animal studies demonstrated the reduction of lung uptake of IMP by administration of large doses of unlabeled IMP, amphetamine, or other amine derivatives (*4,5,15–16*). These observations suggested that the mechanism by which IMP is extracted by the lung from circulation involves a saturable binding process. Although decreased uptake of IMP in the diseased lung lesion was reported (*17*), this cannot explain the variation observed in our study because the examined cases did not show any respiratory symptoms of abnormal chest x-ray.

Recent studies have brought increasing attention to the lung as a metabolic organ (*18*). It has been shown that the lung is an important organ in regulating various vasoactive substances. Different kinetics of IMP in the lung among the subjects may be related to the metabolic functions in the endothelial cells although little is known in this field. Further investigation is necessary to clarify the mechanism of extraction and clearance of IMP in the lung as well as in the brain.

In summary, the lung clearance of IMP showed a great variation among the patients, which influenced the brain uptake. Because of the gradual increase in brain activity after injection of IMP, it is recommended that SPECT data acquisition begin at 20 min. The factors of the lung clearance should be also considered for the assessment of the early and late SPECT scan.

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