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Brain and whole body distribution of *N*-isopropyl-4-iodoamphetamine (I-123) in humans: Comparison of radiopharmaceuticals marketed by different companies in Japan

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Objective: Iodine-123 (^{123}I)-labeled *N*-isopropyl-4-iodoamphetamine (IMP) has been used as a cerebral blood flow (CBF) tracer for single-photon emission computed tomography (SPECT). An autoradiographic (ARG) method has been developed for the quantitation of CBF by IMP and SPECT. Two IMPs (IMP_A and IMP_B) produced by different radiopharmaceutical companies are marketed in Japan. In the present study, whole-body distributions including brain and blood of the two IMPs were compared in the same human subjects. ***Methods:*** Two brain SPECT studies using IMP_A or IMP_B were performed on separate days in six young healthy men. Whole-body scans were also obtained with a large field-of-view single-head gamma camera. One-point arterial blood sampling was performed at 10 min after injection of IMP to measure both the radioactivity concentrations of whole blood and of octanol-extracted components. ***Results:*** No significant differences between the two tracers were observed in body distribution, tracer kinetics in brain, or regional distribution in brain. However, the octanol extraction fraction in blood was significantly different between the two tracers. Radiochemical purity was slightly but significantly different between the tracers. ***Conclusions:*** In the ARG method, arterial input function is determined by calibration of a standard input function with the radioactivity concentration of arterial whole blood. Because the standard input function in the ARG method was obtained using IMP_A, the standard input function obtained for IMP_B should be used when CBF is calculated by the ARG method with IMP_B.

Key words: IMP, SPECT, CBF, ARG method

INTRODUCTION

Iodine-123 (^{123}I)-labeled *N*-isopropyl-4-iodoamphetamine (IMP) has been used as a cerebral blood flow (CBF) tracer for single-photon emission computed tomography (SPECT) on the basis of its large first-pass extraction fraction and high affinity for the brain.[1–3] To quantitate CBF by IMP and SPECT, an autoradiographic (ARG) method has been developed,[4–6] and it is used widely to measure the CBF response to acetazolamide stress.[7] In the ARG method, CBF is calculated from the brain counts of the SPECT scan with an assumed distribution volume value of IMP. The arterial input function is determined by calibration of a standard input function with the radioactivity concentration of arterial whole blood sampled at 10 min after IMP infusion.

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An IMP (IMP_A) has been marketed by a radiopharmaceutical company in Japan since the 1980s. Recently, a generic radiopharmaceutical IMP (IMP_B) was also released by another company in Japan. IMP_A and IMP_B should both possess the same radiochemical aspects, and should also be expected to display the same biodistribution in humans. However, no direct comparison of these tracers with respect to human biodistribution has been reported. In addition, the ARG method was developed with IMP_A using a standard curve of octanol extraction fraction of arterial whole blood determined from 12 human subjects in whom IMP_A was used. In the present study, whole-body distributions of both IMP_A and IMP_B including regional distributions in the brain were compared in the same human subject. To evaluate if the ARG method can also apply to IMP_B, the octanol extraction fractions of arterial whole blood after infusion of IMP_A and IMP_B were also determined and compared.

MATERIALS AND METHODS

Subjects

Six healthy men (20–23 years of age) were recruited to participate in the study, and their written informed consent was obtained. The subjects were judged to be healthy on the basis of their medical history, a physical examination, blood screening, and magnetic resonance (MR) imaging of the brain. The study protocol was approved by the Ethics Committee of Tohoku University Hospital.

Brain SPECT study

Two SPECT studies using IMP_A and IMP_B, respectively, were performed on separate days. The interval between the 2 studies was 7 days. Studies were performed first using IMP_A and then IMP_B in 3 subjects, and first using IMP_B and then IMP_A in the other 3 subjects. A SPECT scanner (SPECT-2000H, Hitachi Medico Corp., Tokyo, Japan),[8] with a four-head rotating gamma camera fitted with low-energy, medium-resolution collimators and in-plane and axial resolutions of 10-mm full width at half maximum (FWHM) was used for all measurements. A dynamic SPECT scan was initiated following intravenous infusion of 102–140 MBq of IMP lasting 1 min. The dynamic scan sequence consisted of 16 200-sec scans with 360° continuous camera rotation. Static SPECT scans were performed at each mid-scan time of 120 min and 180 min after the injection. The static SPECT scan protocol acquired 64 projections at 25 sec with 360° continuous camera rotation (total acquisition time of 1600 sec). One-point arterial blood sampling from the brachial artery was performed at 10 min after the start of IMP infusion to measure both the radioactivity concentrations of whole blood and of the octanol-extracted components from whole blood. Arterial blood gases were also measured. Images were reconstructed by filtered backprojection with a Butterworth filter, and attenuation correction was done numerically by assuming the object to be elliptical for each slice and the attenuation coefficient to be uniform (0.08 cm^{-1}).[9,10] Correction for scattered photons was not performed. Image slices were set up parallel to the orbito-meatal line and were obtained through the whole brain. A cross-calibration scan was performed with the use of a cylindrical uniform phantom (inner diameter, 16 cm) for calibrating the sensitivity between the SPECT scanner and the well-counter system.

Whole-body study

Whole-body scans were obtained with a large field-of-view single-head gamma camera (Hitachi Medico Corp., Tokyo, Japan) fitted with a low-energy, medium-resolution collimator. Anterior whole-body images were acquired lasting 420 sec from 60 min after intravenous infusion of IMP. To calculate the relative tissue radioactivities as a percentage of the injected dose, a standard ^{123}I point source was also scanned.

Measurement of radiochemical purity

Radiochemical purity of IMP (IMP_A and IMP_B) was determined by the thin-layer chromatography (TLC) method in 3 subjects. One microliter of IMP was spotted on a prelayered silica gel $60F_{254}$ TLC plate (Merck KGaA, Damstadt, Germany). The plate was developed in a chloroform, methanol, and acetic acid (84:15:1) solvent system. After development, the plate was dried and placed in contact with a BAS-SR2025 imaging plate (Fuji Photo Film Co., Ltd., Tokyo, Japan). The imaging plate was read using a BAS1800 bioimaging analyzer (Fuji Photo Film).

Data analysis

Static SPECT images at 40 min of mid-scan time were obtained by summation of the frames from 1600 to 3200 sec of dynamic SPECT scan. All static and dynamic SPECT images were transformed into standard brain size and shape by linear and nonlinear parameters with the statistical parametric mapping (SPM2) system for anatomic standardization.[11] Thus, the SPECT images of all subjects had the same anatomic format. Regions of interest (ROIs) were drawn on all anatomically standardized SPECT images, referring to an anatomically standardized T1-weighted MR image. Circular ROIs were defined for the pons, thalamus, and putamen (16 mm in diameter), and elliptical ROIs were defined for the cerebellar cortex, centrum semiovale, and four neocortical regions representing the frontal, temporal, occipital, and parietal lobes (16 mm × 32 mm). To obtain regional time-activity curves, regional radioactivity was calculated for each frame, corrected for decay, and plotted versus time.

From standardized SPECT images at 40 and 180 min of mid-scan time, three-dimensional Z-score maps of IMP_A minus IMP_B and IMP_B minus IMP_A were created on a pixel-by-pixel basis. Areas on these maps showing a p value of <0.05 with correction of multiple comparison

Fig. 1

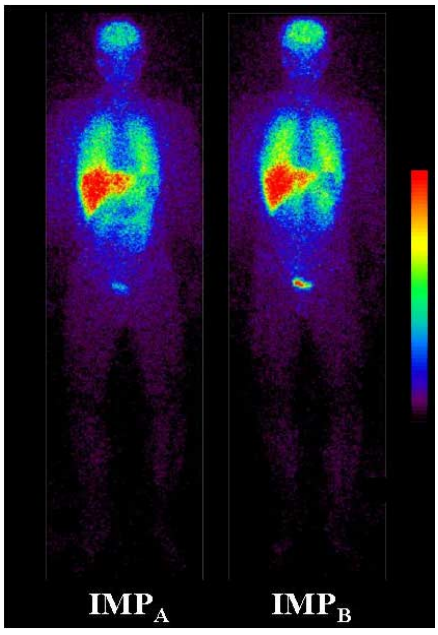

Fig. 2A

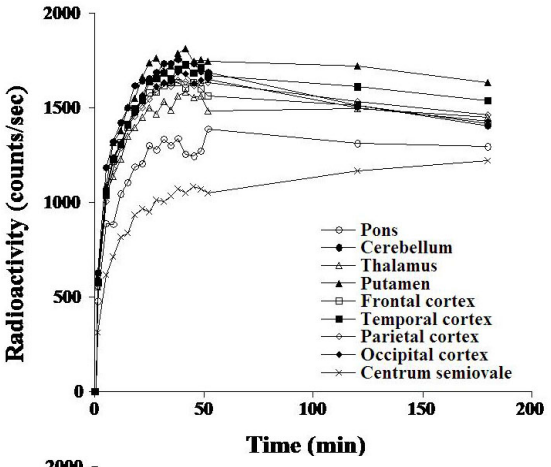

Fig. 2B

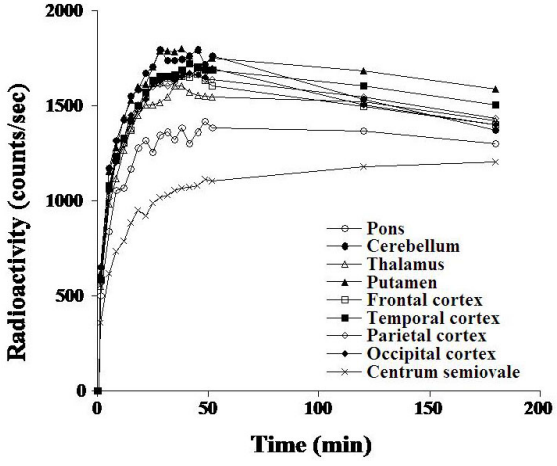

Fig. 1 Typical images of whole-body distribution for IMP_A and IMP_B.

Fig. 2 Average time-activity curves in each brain region for both IMP_A (A) and IMP_B (B). The radioactivity values were converted corresponding to measurements with the well-counter system, and normalized for 111 MBq of injected dose.

Fig. 3A

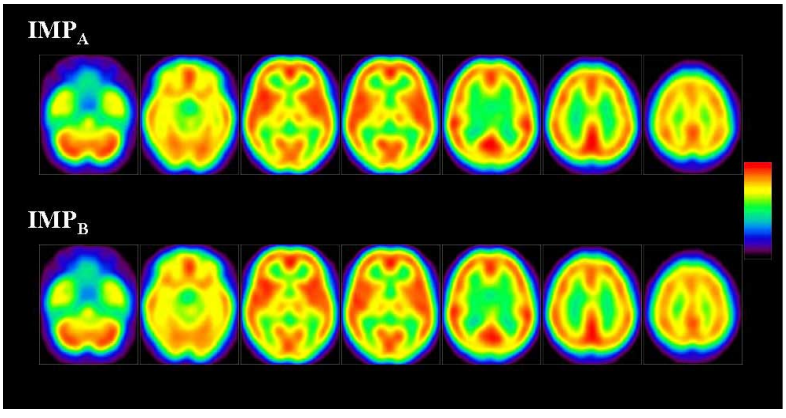

Fig. 3B

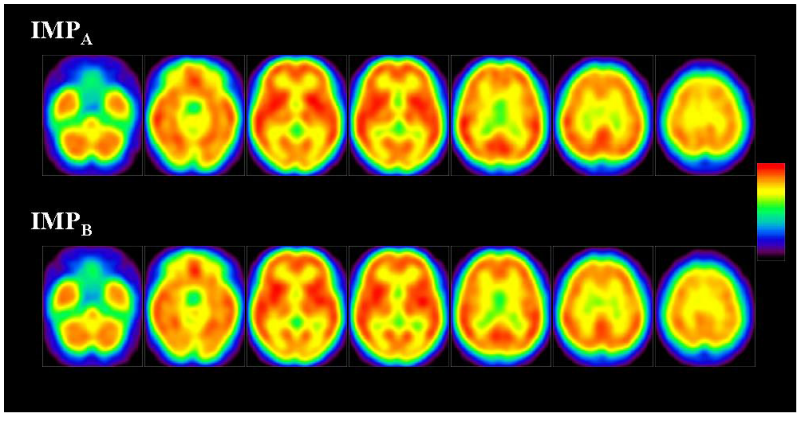

Fig. 3 Average images of standardized SPECT images at 40 min (A) and 180 min (B) of mid-scan time for both IMP_A and IMP_B. All images are transaxial sections parallel to the anterior-posterior commissure (AC-PC) line. The slice positions are −36, −18, 0, 6, 22, 36, and 50 mm from the AC-PC line.

Table 1 P_aCO_2, P_aO_2, pH, blood pressure (BP), and heart rate (HR) in SPECT studies

Study	P_aCO_2 (mm Hg)	P_aO_2 (mm Hg)	pH	BP (Systole/Diastole) (mm Hg)	HR (beats/min)
IMP_A	43.3 ± 1.2	100.0 ± 5.8	7.385 ± 0.024	120 ± 11 / 64 ± 7	67 ± 16
IMP_B	43.4 ± 1.9	105.8 ± 15.3	7.378 ± 0.025	123 ± 4 / 64 ± 2	64 ± 14

Values are mean ± SD

Table 2 Percentage uptake per injected dose of IMP_A and IMP_B for each organ in whole body study

Study	Brain	Lung	Liver
IMP_A	6.5% ± 0.8%	14.0% ± 3.4%	15.9% ± 2.3%
IMP_B	7.0% ± 1.0%	14.6% ± 2.9%	17.0% ± 2.8%

Values are mean ± SD

Table 3 Radioactivity concentrations of arterial whole blood and octanol extracted components per 111 MBq of administered dose, and octanol extraction fraction for both IMP_A and IMP_B

Study	Radioactivity concentration		Extraction fraction
	Whole blood (cps/g)	Octanol-extracted (cps/g)	
IMP_A	191 ± 11	133 ± 9	0.699 ± 0.045
IMP_B	172 ± 21	141 ± 17	0.817 ± 0.046*

Values are mean ± SD
Significant difference between studies (paired t-test, *$p < 0.001$)

Table 4 Radiochemical purity of IMP_A and IMP_B

Subject	IMP_A	IMP_B
1	95.48%	96.36%
2	95.54%	96.48%
3	96.06%	96.46%

were considered to be statistically significant.

ROIs were also drawn on anterior whole-body images. ROIs were defined for contours of the whole brain, lung, and liver. Relative tissue radioactivities as a percentage of the injected dose were calculated for these organs.

RESULTS

Average P_aCO_2, P_aO_2, pH, blood pressure, and heart rate during each SPECT study are given in Table 1. Mean ± SD venous hemoglobin concentration and hematocrit were 14.4 ± 1.0 g/d*l* and 42.6 ± 2.4%, respectively. There were no significant differences in P_aCO_2, P_aO_2, pH, blood pressure or heart rate values between the studies.

Typical images of whole body distribution for both IMP_A and IMP_B are shown in Figure 1. Prominent accumulation was observed in the brain, lung, and liver for both tracers. Percentage uptakes per injected dose of IMP_A and IMP_B in each organ are given in Table 2. No significant differences in uptake were observed between the tracers in any of the organs.

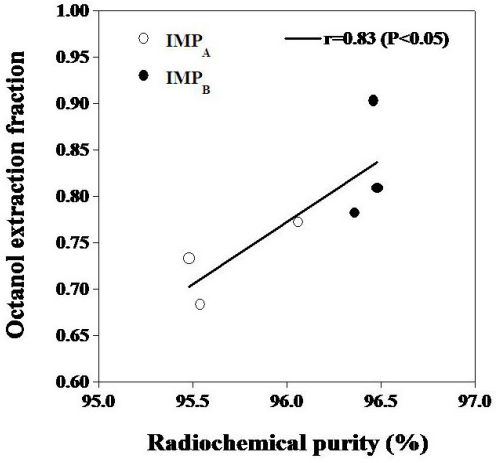

Fig. 4 The correlation between radiochemical purity and octanol extraction fraction of arterial blood samples for IMP_A and IMP_B.

Average time-activity curves in each brain region are shown in Figure 2 for both IMP_A and IMP_B. No significant differences were observed between the tracers in any of the brain regions.

Average images of standardized SPECT images at 40 and 180 min of mid-scan time for both IMP_A and IMP_B are shown in Figure 3. Regional distributions were similar between the two tracers for both SPECT images at 40 and 180 min. On the Z-score images for IMP_A minus IMP_B and IMP_B minus IMP_A, no significant differences were observed in regional accumulation in the brain between the two tracers for both SPECT images at 40 and 180 min.

Radioactivity concentrations of arterial whole blood and octanol-extracted components, and the octanol extraction fraction (ratio of octanol extracted to whole blood counts) for both IMP_A and IMP_B are shown in Table 3. There were no significant differences between the tracers in radioactivity concentrations of arterial whole blood and octanol-extracted components. The octanol extraction fraction of IMP_B was significantly higher than that of IMP_A.

Table 4 shows the radiochemical purity of both IMP_A and IMP_B in 3 subjects. The radiochemical purity of IMP_B was higher than that of IMP_A in all subjects ($p < 0.001$, paired t-test). Significant correlation between radiochemical purity and octanol extraction fraction of arterial blood samples for both IMP_A and IMP_B was observed (Fig. 4).

DISCUSSION

It has been reported that IMP shows high accumulation in the brain, lung, and liver in rat,[1,12] monkey,[2,13] and human.[14] Human brain uptake of IMP has been reported at about 5% per injected dose.[14] In the present study, prominent accumulation was observed in the brain, lung, and liver as previously reported. Brain uptake was 6–7% per injected dose, in good agreement with previously reported values. Although greater accumulation of IMP_B was observed as compared with IMP_A in all organs, the differences were not statistically significant, meaning that whole-body distribution was identical between the tracers.

It is known that radioactivity in human brain rises rapidly after IMP injection and then slowly declines.[14–16] In the present study, brain radioactivity elevated rapidly, peaking at about 40 min in cerebral cortical regions for both tracers, as previously reported. No significant differences in time-activity curves were observed between the two tracers in any brain regions, indicating that the tracer kinetics of IMP_A and IMP_B in the brain is very similar.

In the present study, the two tracers showed similar regional distributions in the brain for the SPECT images at both 40 and 180 min, with no significant differences being observed between them. Recently, in order to investigate changes in the regional distribution of CBF in neurological and psychiatric diseases, statistical analysis on a pixel-by-pixel basis, which requires anatomic standardization techniques and the database of normal distribution of CBF, has been widely applied.[17–19] The present results indicate that such analysis can be performed even if both tracers are used in a subject group.

Although no significant differences were observed between tracers in radioactivity concentrations of arterial whole blood and octanol-extracted components, whole blood radioactivity was lower in IMP_B than in IMP_A, and octanol-extracted radioactivity was higher in IMP_B than in IMP_A. As a consequence, the octanol extraction fraction of IMP_B was significantly higher than that of IMP_A. The metabolic pathway of IMP in plasma has been reported.[20] IMP is sequentially metabolized into *p*-iodoamphetamine (PIA), *p*-iodophenylacetone (PIPA), *p*-iodobenzoic acid (PIB), and then *p*-iodohippuric acid (PIH). Because PIB and PIH are water-soluble metabolites and the fraction of PIPA is negligibly small, the octanol-extracted components were considered to be IMP and PIA. To our knowledge, the reason for the difference in the octanol extraction fraction between the two tracers has not been reported. Some factors of IMP, such as radiochemical purity and solvent composition, might be involved.

The radiochemical purity of IMP_B was slightly but significantly higher than that of IMP_A, and there was a significant correlation between the radiochemical purity and the octanol extraction fraction. The radioactivity concentration in blood per injected dose of IMP within one hour post injection in mice was more than ten times lower than that of iodine ion (I^-),[1,21] indicating that the clearance rate of IMP in blood is rapid as compared with I^-. This might explain why the radiochemical purity of IMP was correlated with the octanol extraction fraction.

When quantitatively assessing CBF by the ARG method, arterial input function is determined by calibration of a standard input function using the radioactivity concentration of arterial whole blood sampled at 10 min after IMP infusion.[4–6] Because the standard input function in the ARG method, which corresponds to the standard curve of arterial whole blood radioactivity multiplied by the standard curve of the octanol extraction fraction, was obtained using IMP_A,[4] this ARG method cannot be used for IMP_B. According to the present results of octanol extraction fraction for IMP_A and IMP_B, CBF calculated by this ARG method with IMP_B would be overestimated by about 15% as well as the distribution volume. The standard input function obtained for IMP_B should be used when CBF is calculated by the ARG method with IMP_B.

In conclusion, the whole-body distributions including brain and blood of the two IMPs (IMP_A and IMP_B) produced by different radiopharmaceutical companies in Japan were compared in the same human subjects. No significant differences between the two tracers were observed in terms of whole-body distribution, tracer kinetics in brain, or regional distribution in brain. However, the octanol extraction fraction in blood was significantly different between the tracers, and radiochemical purity was slightly but significantly different between them. In the ARG method, the arterial input function is determined by calibration of a standard input function with radioactivity concentration of arterial whole blood. Because the standard input function in the ARG method was obtained using IMP_A, the standard input function obtained for IMP_B should be used when CBF is calculated by the ARG method with IMP_B.

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