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Iodine-123 iodobenzofuran (I-123 IBF) SPECT in patients with parkinsonism

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I-123 IBF is a dopaminergic antagonist which is suitable for SPECT imaging of D2 receptors. The purpose of this study is to evaluate the potential usefulness of semi-quantitative parameters obtained from brain SPECT data of I-123 IBF for differential diagnosis in patients with parkinsonism (PN). Subjects were 10 patients with PN: 2 patients with striato-nigral degeneration (SND), 5 patients with Parkinson's disease (PD), 2 patients with progressive supranuclear palsy (PSP) and one patient with olivo-ponto-cerebellar atrophy (OPCA). The data were acquired with a triple-head gamma camera at 2 hours after intravenous injection of 167 MBq of I-123 IBF. Transverse images were reconstructed by means of filtered backprojection, and attenuation correction was performed by Chang's method ($\mu = 0.08$). The basal ganglia-to-frontal cortex ratio (GFR) and the basal ganglia-to-occipital cortex ratio(GOR) on slices of 5 different thicknesses were calculated. The GFR and GOR were lower in the SND group than in the other disease groups in all slices with different thicknesses (7.2 mm, 14.4 mm, 21.6 mm, 28.8 mm and 43.2 mm). The semiquantitative parameters (GFR and GOR) obtained from brain SPECT data at 2 hours after intravenous injection of I-123 IBF may be useful for differential diagnosis in patients with PN.

Key words: I-123 IBF, parkinsonism, SPECT

INTRODUCTION

SEVERAL IODINATED substituted benzamides for brain D2 receptors were recently proposed.[1–10] Iodine-123 iodobenzamide (I-123 IBZM), which was the first compound of this class, had been used for evaluation of D2-receptor related diseases, such as Parkinson's disease, Huntington's disease, progressive supranuclear palsy and schizophrenia.[1–7] Later, Iodine-123 benzofuran (I-123 IBF) was developed as a potential SPECT tracer.[8] I-123 IBF exhibited higher affinities for D2 receptors and produced higher target-to-background ratios than I-123 IBZM did.[8–10] Simple region of interest (ROI) studies were used in previous studies.[2–7,10,15] In most of them,[2–5,7,15] the templates of ROIs were used in order to avoid the changes in values due to the size of the ROI. We also used, the templates of ROIs in our study.

The purpose of this study is to evaluate the potential usefulness of semi-quantitative parameters obtained from brain SPECT data 2 hours after intravenous injection of I-123 IBF for differential diagnosis in patients with parkinsonism (PN), and to estimate how parameters are affected by the thickness of slices under the conditions in which the sizes of ROIs were fixed.

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MATERIALS AND METHODS

I-123 IBF

I-123 IBF was obtained from Nihon Medi-Physics Co., Ltd. (Hyogo, Japan). It was prepared at 111 MBq/m*l* with 0.50 mg/m*l* of IBF. Specific activity was 88,800 GBq (2,400 Ci)/mmol. Each vial contained 167 MBq of I-123 IBF and 0.75 μg of IBF.

Patients (Table 1)

We studied 10 patients (six men and four women; mean age 63 ± 9.8 years, range 49–78) with PN; 2 patients with

Table 1 Clinical data of 10 patients with parkinsonism

Patient No.	Sex	Age	Disease	HY scale	Drugs		Duration of the disease (years)	Findings of CT or MRI
					L-dopa	ACD		
1	M	49	SND	2	Ineffective	Effective	5	Atrophy of the frontal lobes
2	F	59	SND	3	Insufficient	Insufficient	3	Atrophy of the temporal lobes
3	M	57	PD	2	Effective	Effective	4	Atrophy of the temporal lobes
4	F	78	PD	3	Effective	—	9	Atrophy of the frontal lobes Lacunar infarction
5	M	73	PD	2	Effective	Insufficient	3	Lacunar infarction
6	F	58	PD	4	Effective	Insufficient	20	WNL
7	M	57	PD	3	Effective	Insufficient	13	WNL
8	F	62	PSP	3	—	—	2	Atrophy of the midbrain
9	M	60	PSP	2	—	—	1	Atrophy of the midbrain Lacunar infarction
10	M	78	OPCA	2	—	—	1	Atrophy of the pons and cerebellum

SND; striato-nigral degeneration, PD; Parkinson's disease, PSP; progressive supranuclear palsy, OPCA; olivo-ponto-cerebellar atrophy, ACD; anticholinergic drug, HY scale; Hoehn-Yahr scale, WNL; within normal limits

Table 2 Mean values of parameters (GFR and GOR) in patients with PD, SND, PSP and OPCA

Disease (No. of Patient)	Method (thickness) mm	GFR	GOR
SND (2)	A 7.2	0.43 ± 0.02	0.59 ± 0.05
	B 14.4	0.37 ± 0.09	0.63 ± 0.08
	C 21.6	0.39 ± 0.11	0.55 ± 0.03
	D 28.8	0.31 ± 0.03	0.49 ± 0.07
	E 43.2	0.29 ± 0.02	0.35 ± 0.06
PD (5)	A 7.2	0.97 ± 0.20	1.02 ± 0.14
	B 14.4	0.92 ± 0.14	0.97 ± 0.14
	C 21.6	0.86 ± 0.20	0.92 ± 0.09
	D 28.8	0.77 ± 0.19	0.86 ± 0.14
	E 43.2	0.61 ± 0.14	0.67 ± 0.14
PSP (2)	A 7.2	0.83 ± 0.14	1.09 ± 0.12
	B 14.4	0.80 ± 0.11	1.05 ± 0.25
	C 21.6	0.72 ± 0.14	0.89 ± 0.24
	D 28.8	0.65 ± 0.11	0.86 ± 0.17
	E 43.2	0.51 ± 0.14	0.35 ± 0.12
OPCA (1)	A 7.2	1.04	1.22
	B 14.4	1.00	1.20
	C 21.6	0.89	1.06
	D 28.8	0.80	0.92
	E 43.2	0.61	0.71

striato-nigral degeneration (SND), 5 patients with Parkinson's disease (PD), 2 patients with progressive supranuclear palsy (PSP) and one patient with olivo-ponto-cerebellar atrophy (OPCA). Before this study, we had obtained permission for the clinical use of I-123 IBF from the committee on drug diagnosis and therapeutic study at Kagoshima University Hospital, and all patients gave informed consent. The duration of the disease was 6.1 ± 6.0 years and the score on the Hoehn-Yahr scale was 2.6 ± 0.70 (mean ± s.d.). Two patients had a diagnosis of

Table 3 The values of the %difference of GFR and GOR between PD and SND at each slice thickness

Thickness of slice mm	GFR %	GOR %
A 7.2	56	42
B 14.4	60	35
C 21.6	55	40
D 28.8	60	43
E 43.2	52	48

SND with a disease duration of 5 and 3 years, and a score on the Hoehn-Yahr scale of 2 and 3. Five patients had a diagnosis of PD with a disease duration of 9.7 ± 6.8 years and a score on the Hoehn-Yahr scale of 2.8 ± 0.84. Two patients had a diagnosis of PSP with a disease duration of 2 years and one year, and a score on the Hoehn-Yahr scale of 3 and 2. A 78-year-old man had a diagnosis of OPCA with a disease duration of one year and a score on the Hoehn-Yahr scale of 2.

The diagnosis was based on history, clinical symptoms, response to L-dopa therapy and CT or MRI finding information in all patients. Seven of ten patients were given L-dopa. The administration of L-dopa drugs was stopped prior to 20 hours before the SPECT imaging in two of the seven patients and not stopped in the other five patients. MRI or CT was performed within 2.5 months after or before the administration of I-123 IBF.

SPECT study

Three hundred mg of potassium iodide per day was orally given to each patient from one day before to one day after the study to protect the thyroid gland from the uptake of free I-123. I-123 IBF (167 MBq) was intravenously injected as a bolus within a few seconds. The SPECT data were acquired once at 110–130 min, after i.v. injection of I-123 IBF, with a triple-head rotating gamma camera with

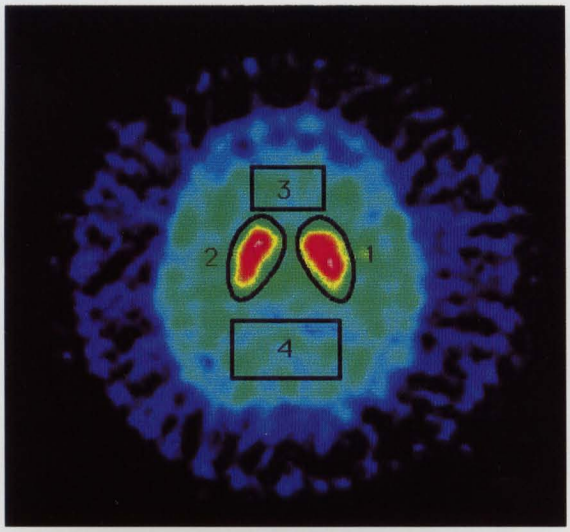


Fig. 1 The ROIs of the left (1) and right ganglia (2), frontal cortex (3), occipital cortex (4) to use as the templetes (Patient 4, Parkinson's disease).

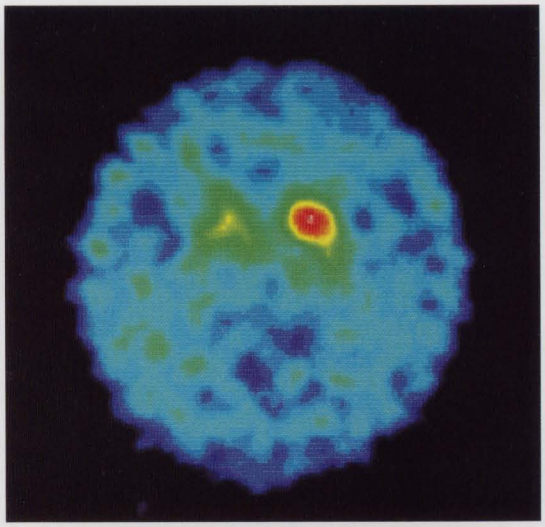
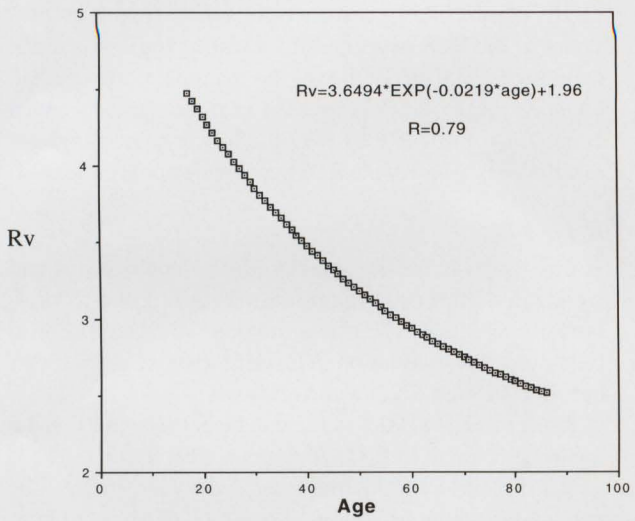
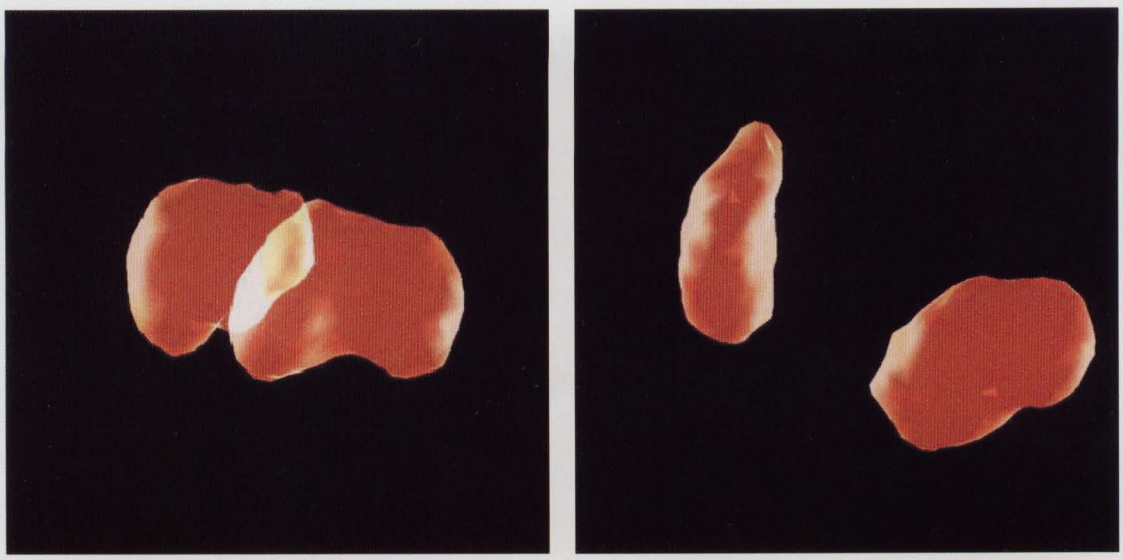


Fig. 2 An I-123 IBF SPECT image of a 59-year-old woman (Patient 2) with SND.



◀ **Fig. 3** An example of the relationship between Rv (a parameter of D2 binding) and age. The curve was obtained from the regression equation by an exponential model for the caudate, which Ichise et al. had reported.[14]

▼ **Fig. 4** Three dimensional display of the left and right basal ganglia in a patient with Parkinson's disease (Patient 4).



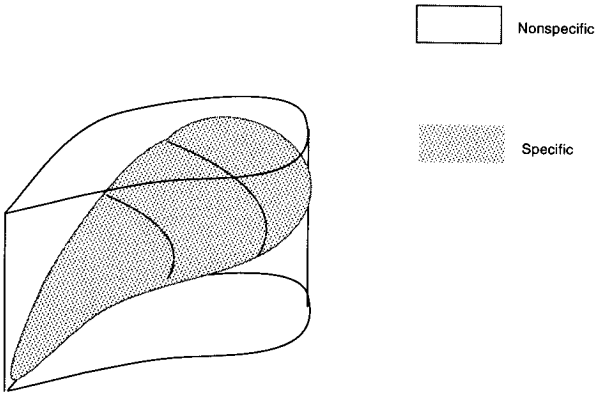


Fig. 5 The schema shows the relationship between the three dimensional shape of ROI and the basal ganglion. Three dimensional shape of ROI is like a pole whose transverse shape is the template of the ganglion ROI. The rate of the volume which contains D2-receptors to the whole volume of ROI, decreases with increase in slice thickness.

fanbeam high-resolution collimators and 159 keV ± 10% of the photo window in 90 projections with 360° rotation (128 × 128 matrix). Each scan was performed in order to obtain transverse images which were parallel to the orbitomeatal line.

Image reconstruction

The raw projection data were prefiltered with a Butterworth filter (cutoff frequency: 0.13 cycle/pixel; power factor: 8). The SPECT images were then reconstructed by means of a filtered back projection algorithm with a Ramp filter. Attenuation correction was performed by assuming an elliptical outline of the head in each slice and uniform attenuation in the head ($\mu = 0.08$). The transaxial images 7.2 mm thick were displayed as the original slices for ROI study.

ROI study

In order to evaluate the effects of slice thickness on the results for parameters, slices of 5 different thicknesses were prepared individually.

Thickness of slice for ROI study

The ganglia were visualized within six original contiguous slices each 7.2 mm thick in all patients. The ROI studies were performed on 5 slices of different thicknesses in which the basal ganglia were most clearly visualized in each patient. The slice thickness was as follows: A, 7.2 mm; B, 14.4 mm; C, 21.6 mm; D, 28.8 mm and E, 43.2 mm. All selections were performed visually by one observer (Y.N.).

ROIs

A slice in which the basal ganglia were the largest was selected visually out of the all 7.2 mm thick slices for all ten patients, and irregular ROIs over the left (13.81 cm^2) and right (11.85 cm^2) basal ganglia and rectangular ROIs over the frontal (8.52 cm^2) and occipital (17.14 cm^2) cortex were drawn manually (Fig. 1). These ROIs were fixed and used as templates of ROIs for all the other slices regardless of the slice thickness in all patients. When the ROIs were adapted to the lesions, only linear movement of ROIs was permitted in the up, down, left or right direction. No rotation of the ROIs or change in the ROI size was performed. All maneuvers in adapting templates of the ROIs to the lesions were performed by one observer (Y.N.).

The definition of parameters was as follows:

The basal ganglia-to-frontal cortex ratio (GFR) = left GFR + right GFR;[7] left or right GFR: (mean counts/voxel of the ROI over the left or right ganglion – mean counts/voxel of the ROI over the frontal cortex)/mean counts/voxel of the ROI over the frontal cortex = mean counts/voxel of the ROI over the left or right ganglion/mean counts/voxel of the ROI over the frontal cortex – 1.

The basal ganglia-to-occipital cortex ratio (GOR) = left GOR + right GOR;[7] left or right GOR: (mean counts/voxel of the ROI over the left or right ganglion – mean counts/voxel of the ROI over the occipital cortex)/mean counts/voxel of the ROI over the occipital cortex = mean counts/voxel of the ROI over the left or right ganglion/mean counts/voxel of the ROI over the occipital cortex – 1.

%diff

In order to evaluate the potency of parameters (GFR and GOR) in differential diagnosis, % difference (%diff) between PD and SND was introduced as a potential parameter for evaluation. The definition of each %diff between PD and SND was as follows:

%diff (GFR) = 100 × (the mean GFR value in PD – the mean GFR value in SND)/the mean GFR value in PD,

%diff (GOR) = 100 × (the mean GOR value in PD – the mean GOR value in SND)/the mean GOR value in PD.

RESULTS

No side effect was observed after the intravenous administration of I-123 IBF. Table 2 shows the mean values for each disease in each slice of different thicknessess (A–E). The mean GFR and GOR values were definitely lower in the SND patient group than in the other disease patient groups in all slices of different thicknessess (A–E). A representative image (slice thickness, 7.2 mm) of SND (Patients 2) is shown in Fig. 2. All values were reduced with the increase in slice thickness. Table 3 shows the %diff between PD and SND for each parameter in each slice of different thickness. The value was larger in GFR than in GOR at each thickness. The variation in slice thickness was less in GFR than in GOR.

DISCUSSION

In this study, the simple ROI count methods were used. A noninvasive method and short sampling time are desirable in order to use I-123 IBF clinically. The results of this simple ROI count method might be affected by intersubject differences in factors not related to the receptors, such as peripheral clearance, nonspecific binding to plasma proteins or cerebral tissue and cerebral blood flow.[11] In order to avoid these effects, model-based methods were reported, which characterized the regional responses to the arterial input function and provided quantitative estimation of receptor parameters,[11] but in this kinetic method, arterial sampling is needed.

Ichise et al. reported a method for measuring the receptor parameter k_3/k_4, the ratio of the transfer constants for the intracerebral nondisplaceable and specifically bound receptor compartments, by means of a variation of the graphical analysis method that derives the ratio of ligand distribution volume ($Rv = V_3/V_4$) from serial SPECT without arterial blood sampling,[12] but it needs continuous SPECT scanning for at least 2 hr to obtain the state value of parameters.[12] Afterwards, a more simplified method was reported to obtain the same outcomes using three separate 20-min scans.[13] Even this simplified method may be difficult to use in some patients with PN who are elderly, agitated or have hyperkinetic movement. The basal ganglia-to-cerebellum ratio is typically used to analyze data,[1,3,8,10] but the cerebellum is difficult to localize exactly without CT or MRI coregistration. In baboon, intravenous injection of a receptor saturating dose of unlabeled raclopride did not produce any displacement of activity in the occipital cortex, so the occipital region contains only a negligible concentration of D2 receptors.[11] The GOR was therefore used in some reports.[5,10] The GFR was also used as a parameter of D2 receptors.[3,4,6,13,14] We also employed these parameters for semiquantitative estimation of D2 receptor availability for I-123 IBF binding.[7] Ichise et al. reported that D2 binding declined with age, equally for the caudate nucleus and putamen at 7%–13% per decade and that the decline was progressively smaller with age[14] (Fig. 3). The mean ages of patients in each disease in our study were: 54 ± 7 years in SND, 65 ± 10 years in PD, 61 ± 1 in PSP and 78 in OPCA. Despite the youngest age, definitely lower mean GFR and GOR were found in patients with SND than in patients with PD, PSP and OPCA in our study. Buck et al. reported that the GFR was the same or a little increased in PD patients, decreased in patients with multiple systemic atrophy (MSA), and also decreased in PSP patients when compared with normal controls.[15] In our study, although there were no normal controls, the results in patients with PD, and SND which belongs to MSA, were consistent with their study. In PSP patients, the values decreased slightly in the GFR, but did not decrease in the GOR when compared with those of PD and OPCA patients. Further examination may be needed. A sufficient slice thickness containing basal ganglia is needed to evaluate D2 receptors as a whole. The values for each parameter were reduced with the increase in slice thickness in our study. In this method, the three dimensional shape of ROI is like a pole whose transverse shape is the same as each irregular ROI over the basal ganglion, but the three dimensional shape of the basal ganglion is not like a pole (Fig. 4). Therefore the proportion of the volume which contains few receptors, to the whole volume of ROI, increases with the increase in slice thickness (Fig. 5). The higher the %diff between PD and SND suggests a higher potential for differential diagnosis in patients with PN. Higher %diff values were obtained in the GFR than in the GOR in all slices with different thicknesses. This method is simple and suitable for clinical use, but in this method, the ROI over the occipital or frontal cortex may contain a part of the bilateral lateral ventricules. Therefore the size of the bilateral lateral ventricules may affect the results for GFR or GFR. As the values for %diff in the GFR and GOR were relatively constant, the slice thickness may not be a significant factor influencing the clinical value of these parameters.

CONCLUSION

The empiric quantitative parameters (the GFR and GOR) obtained from brain SPECT data 2 hours after venous injection of I-123 IBF may be useful for differential diagnosis in patients with PN.

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