Iodine-123-Iomazenil and Iodine-123-Iodoamphetamine SPECT in Major Cerebral Artery Occlusive Disease

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Iodine-123-iomazenil (IMZ) is a SPECT ligand for central-type benzodiazepine receptors, which are located only on neurons. We evaluated the feasibility of using IMZ SPECT for identifying neuronal damage in patients with the chronic phase of thrombotic cerebral ischemia. **Methods:** We studied 15 patients with angiographically-confirmed unilateral severe occlusive lesions (occlusion or > 70% stenosis) in the carotid system. IMZ SPECT images obtained 180 min after injection of 167–222 MBq IMZ were analyzed. The regional cerebral blood flow and perfusion reserve were evaluated for comparison with IMZ SPECT findings, using the split-dose ^{123}I-iodoamphetamine (IMP) SPECT method, coupled with intravenous injection of 1 g acetazolamide. On both SPECT images, the count ratio of the affected to the nonaffected whole MCA territory (A/NA ratio) and of the contralateral to the ipsilateral cerebellar cortex (C/I ratio) were determined. **Results:** The A/NA ratio with IMZ was significantly higher than that with IMP (94.5% ± 6.2% versus 91.4% ± 6.6%, $p < 0.005$), although a significantly positive correlation was found between these two ratios ($r = 0.854$, $p < 0.0001$). The C/I ratio with IMP was decreased significantly in 5 patients compared with that in normal subjects, whereas the C/I ratio with IMZ was decreased in only 1 patient. There was no significant correlation between the A/NA ratio with IMZ and the perfusion reserve in the affected MCA territory. In 2 of 5 patients with a decreased A/NA ratio (<90%) with IMZ, decreased blood flow with preserved perfusion reserve and cerebral hemispheric atrophy were observed, which suggested the influence of neuronal loss due to chronic ischemia. **Conclusion:** These findings indicate that IMZ SPECT, which provides new information regarding neuronal damage after ischemic insult to the brain, is useful for evaluating thrombotic cerebral ischemia.

Key Words: iodine-123-iomazenil; SPECT; cerebral ischemia; diaschisis; perfusion reserve

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Several imaging techniques such as x-ray CT, MRI and perfusion and metabolism imaging have been used to visualize ischemic damage to the brain (*1–4*). However, these imaging modalities are unable to provide direct findings concerning neuron-specific damage after ischemic insults.

Iodine-123 Ro 16-0154 (ethyl-5,6-dihydro-7-iodo-5-methyl-6-oxo-4H-imidazo[1,5-a] [1,4]-benzodiazepine-3-carboxylate; iomazenil) is a specific ligand for central-type benzodiazepine receptors, which are located only on neurons (*5,6*). Iodine-123-iomazenil (IMZ) has favorable characteristics for in vivo assessment of benzodiazepine receptors with SPECT, including high brain uptake, little nonspecific binding and high affinity for receptors (*7*). Several studies have been performed to determine the clinical usefulness of IMZ SPECT in Alzheimer's disease (*8,9*), epilepsy (*8,10*) and psychiatric disease (*11*). However, to the best of our knowledge, there have been only a few experimental (*12*) and clinical (*13,14*) studies evaluating the usefulness of IMZ in cerebral ischemia.

The purpose of this study was to evaluate the feasibility of IMZ SPECT for identifying neuronal damage in the brains of patients with thrombotic cerebral ischemia. We compared the results of IMZ SPECT with regional cerebral blood flow (rCBF) and cerebral perfusion reserve which were determined by the split-dose ^{123}I-iodoamphetamine (IMP) SPECT method (*3*) coupled with acetazolamide challenge.

MATERIALS AND METHODS

Patients

Fifteen patients (14 men, 1 woman; mean ± s.d. age 57.6 ± 7.5 yr) with unilateral occlusion or severe stenosis (>70% in diameter) of the internal carotid artery (ICA), the common carotid artery (CCA) or the main trunk of the middle cerebral artery (MCA) were examined. The vascular lesions were in the ICA in 6 patients, the CCA in 1 and the main trunk of the MCA in 8 patients. Brain MRI, cerebral angiography, IMZ SPECT and IMP SPECT with acetazolamide challenge were performed in all patients. Clinical diagnoses were silent cerebral infarction in 2 patients, transient ischemic attacks in 4 and completed stroke in 9 (*15*). All symptoms of 13 symptomatic patients were referable to their vascular lesions. The remaining 2 patients, who complained of nonfocal neurological symptoms of dizziness or headache, exhibited infarctions in the cerebral hemisphere ipsilateral to the vascular lesions. At the time of the IMZ study, 9 patients suffered from hemiparesis or sensory impairment on the side contralateral to their vascular lesions. An associated cortical sign was present for only 1 patient (Patient 9), who exhibited motor aphasia. Patients who had a cardioembolic risk factor, such as atrial fibrillation, valvular heart disease or myocardial infarction, were excluded (*15*).

In 13 symptomatic patients, the interval between the onset of each symptom and IMZ SPECT study was from 47 days to 9 yr. In 2 asymptomatic patients, the interval between angiography and IMZ SPECT study was 3 mo and 1.5 yr. Twelve patients exhibited infarction on MRI, including 6 cortical and 10 subcortical lesions on the side ipsilateral to the vascular lesions, while no ischemic lesions were found in the contralateral hemispheres. Three patients had no infarction on MRI. Patients were classified into two groups: with cortical lesions (n = 6) and without cortical lesions (n = 9). The clinical and neuroradiological findings for each patient are summarized in Table 1. No patient had a cerebellar lesion revealed by neurological and MRI studies.

No patient had been treated with a benzodiazepine receptor agonist such as diazepam before the IMZ study. The study protocol

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TABLE 1
Clinical and Neuroradiological Findings

Patient no.	Age (yr)	Sex	Clinical diagnosis	Duration of disease	Neurological signs at time of IMZ study	MRI lesions	Angiographic findings
1	62	M	Asymptomatic	3 mo	None	Cortical (R frontal)	R ICA O
2	67	M	Asymptomatic	1.5 yr	None	Cortical (R temporal)	R ICA O
3	65	M	TIA	3.2 yr	None	Subcortical (R BG)	R MCA S (70%)
4	59	M	TIA	2 yr	None	None	L CCA O
5	52	M	TIA	3 yr	None	None	R ICA O
6	39	M	TIA	3 yr	None	None	L MCA S (90%)
7	58	M	CS	47 days	L sensory impairment	Subcortical (R corona radiata)	R MCA S (99%)
8	58	M	CS	47 days	L hemi	Cortical (R temporal), subcortical (R corona radiata)	R MCA O
9	53	F	CS	6 yr	R hemi, motor aphasia	Subcortical (L corona radiata)	L ICA S (90%)
10	55	M	CS	1 yr	R hemi	Subcortical (L frontal)	L ICA O
11	51	M	CS	2 yr	L sensory impairment	Cortical (R temporal), subcortical (R BG)	R MCA S (90%)
12	59	M	CS	4 yr	R hemi	Cortical (L posterior watershed), subcortical (L BG)	L MCA O
13	55	M	CS	4 yr	R hemi	Subcortical (L corona radiata, L BG)	L MCA S (70%)
14	61	M	CS	6 yr	L hemi	Subcortical (R corona radiata)	R MCA S (90%)
15	70	M	CS	9 yr	L hemi	Cortical (R posterior watershed)	R ICA S (90%)

TIA = transient ischemic attack; CS = completed stroke; L = left; R = right; hemi = hemiparesis; BG = basal ganglia; ICA = internal carotid artery; MCA = middle cerebral artery; CCA = common carotid artery; O = occlusion; S = stenosis

was in accordance with the standard ethical guidelines of Osaka University Medical School, and written informed consent was obtained from all patients before the study.

Brain MRI Scan

MRI was performed before the IMZ SPECT study with a 1.5-T unit (Magnetom; Siemens, Munich, Bavaria, Germany) in the orbito-meatal (OM) plane with 5-mm-thick sections. Infarction was defined as a focal area with prolonged T1 and T2 relaxation times larger than 5 mm in diameter (*16*).

Angiography

Angiography was performed using conventional techniques for six patients, and intra-arterial digital subtraction angiography for nine patients. The presence of steno-occlusive lesions of the major cerebral arteries was determined (*4*).

SPECT Procedure for IMZ

Patients received 167–222 MBq IMZ by intravenous bolus injection in 1.5 ml of solution into a cubital vein. SPECT imaging was started 180 min after injection, with 11 min of data acquisition. We used a four-head rotating gamma camera equipped with low-energy, general-purpose, parallel-hole collimators with a 13.0-mm FWHM (Gamma View SPECT 2000H; Hitachi Medical Co., Tokyo, Japan). Data were recorded on a 64 × 64 matrix. The 8-mm slice transaxial images were reconstructed using a Butterworth filter as the prefilter and a Ramachandran filter as the reconstruction filter. Chang's postreconstruction attenuation correction was applied with an attenuation coefficient of 0.08 cm^{-1} to the transaxial image data. The plane of IMZ imaging was set parallel to the OM line.

IMP SPECT Study of Cerebral Blood Flow and Perfusion Reserve

The IMP SPECT study was performed within 7 days before and after the IMZ study. During both SPECT studies, no changes in clinical features were found in any of the patients. The details of our IMP SPECT study with acetazolamide challenge have been reported elsewhere (*3*). In brief, we used the same scanner as for the IMZ study along with low-energy, general-purpose, parallel-hole collimators. Data were acquired in a continuous rotating mode in reciprocal directions at 20 sec/revolution for 58 min, 14 frames with 8 revolutions followed by 2 frames with 32 revolutions, from 64 directions in a 64 × 64 matrix. During dynamic SPECT, 111 MBq IMP were injected intravenously at the beginning of imaging and again at the start of the tenth frame of acquisition, with continuous arterial blood sampling for 332 sec after each injection. One gram of acetazolamide was slowly injected intravenously for 1 min, at the start of the fourth frame of acquisition. The absolute rCBF values were quantified by the microsphere method using the octanol extraction activities of arterial samplings (*2*). The resting CBF image was reconstructed from the summation of the second-to-ninth-frame data. The acetazolamide challenge CBF image was reconstructed from the summation of the 11th-to-16th-frame data, with subtraction of the remaining brain activity due to the first IMP injection. On both resting and acetazolamide-challenge CBF images, the 8-mm slice transaxial images were reconstructed, and were adjusted to the OM line.

Evaluation of IMZ, Cerebral Blood Flow and Perfusion Reserve

Regions of interest (ROIs) analysis in this study is illustrated in Figure 1. In transaxial images obtained in the IMZ and IMP studies, the corresponding sets of six consecutive slices from the basal ganglia and thalamic level to the parietal cortex level were selected so as to include most of the MCA territories. Among them, the top three and bottom three slices were added separately to create two integrated images that were outlined using the 50% iso-accumulation line of the maximum value in the slice. The outlined cerebral area was automatically divided into three equal-sized longitudinal ROIs on the top integrated image (Fig. 1A) and into four ROIs on the bottom integrated image (Fig. 1B). Bilateral outer ROIs on each integrated image corresponded to the bilateral MCA territories. If an infarct was included within this standard ROI, the size of the ROI was reduced to avoid the infarct. The accumulations in MCA ROIs were summed over the images and averaged by pixel and slice (*16*). For examination of the cerebellum, two slices including the cerebellum were added, and an irregular ROI encompassing the cerebellar hemisphere was drawn manually (Fig. 1C).

The count ratio of the affected to the nonaffected MCA territory, defined as the A/NA ratio, and the count ratio of the contralateral

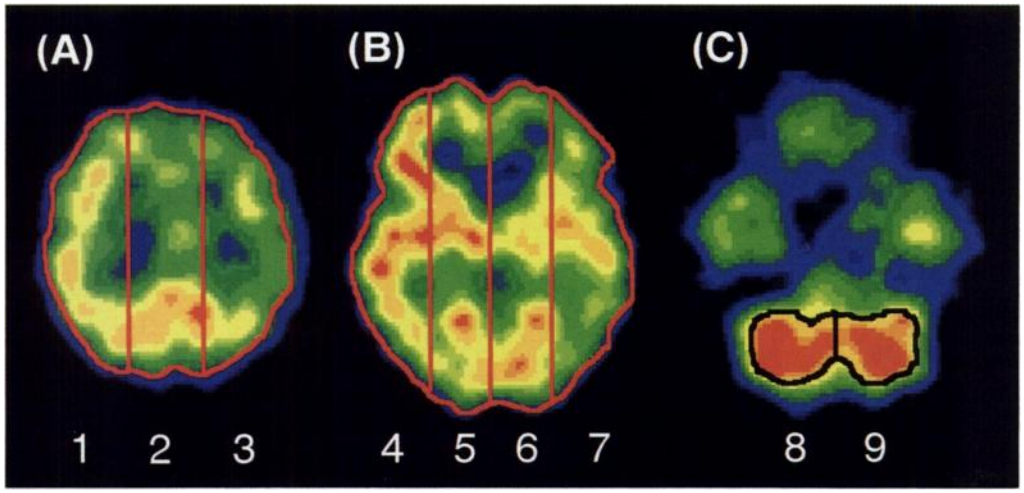

FIGURE 1. ROI used in the SPECT analysis. Automatically drawn ROIs that correspond to the bilateral MCA territories at the parietal lobe level (1 and 3 in Fig. 1A) and thalamic level (4 and 7 in Fig. 1B), respectively. Manually drawn ROIs corresponding to the cerebellar hemisphere (8 and 9 in Fig. 1C).

to the ipsilateral cerebellar cortex, defined as the C/I ratio, were calculated for IMZ and IMP resting state images. The percent increase in rCBF induced by acetazolamide challenge (%INC) was estimated as the vascular perfusion reserve as follows (*3*): %INC = [CBF(ACZ)-CBF(rest)]/CBF(rest) × 100, where CBF (ACZ) and CBF(rest) represent the CBF in the acetazolamide-challenge and in the resting state, respectively.

The normal value of the A/NA ratio with IMZ was determined using published values on normal volunteers (*8*) and was considered to be from 90% to 110%. The normal value of the C/I ratio with IMP was obtained from 10 age-matched normal subjects (9 men and 1 woman; age, 64.8 ± 6.9 yr), from 92.8% (mean −2 s.d.) to 107.2% (mean + 2 s.d.). The normal value of %INC was determined from our previous study (*3*), and patients were classified into two groups: the decreased group having a %INC < 30% and the normal group 30% or higher.

Statistical Analysis

We compared A/NA ratios with IMZ and IMP by paired Student's t-test. We determined the relationships between IMZ A/NA ratio and IMP A/NA ratio, absolute rCBF value, duration of ischemia by linear-regression analysis and Pearson correlation coefficient. A difference of $p < 0.05$ was considered significant. Results are expressed as means ± s.d.

RESULTS

Figure 2 shows results of MRI, IMP in the resting state and the acetazolamide-challenge state, and IMZ images for Patient 9. The patient showed right hemiparesis and motor aphasia, while MRI revealed only subcortical infarct in the left corona radiata with no involvement of the cortical area. IMP SPECT showed widespread and severe low perfusion in the frontal and temporal cortices with decreased perfusion reserve in the left MCA territory (IMP A/NA ratio = 79.2%, %INC = 6.0%). IMZ SPECT revealed low uptake in the left frontal and temporal cortices, including the Broca area that were normal on MRI (IMZ A/NA ratio = 86.1%). The degree of reduction of IMZ uptake in the left MCA territory was smaller than that of IMP in the resting state.

Figure 3A shows the relationship between the IMZ and IMP A/NA ratios in the resting state. The 2 ratios exhibited a significant positive correlation ($r = 0.854$; $p < 0.0001$). In addition, the A/NA ratio with IMZ was significantly higher than that with IMP (94.5% ± 6.2% versus 91.4% ± 6.6%, $p < 0.005$). Figure 3B shows a comparison of IMZ and IMP C/I ratios in the resting state. There was no significant correlation between these ratios. In 5 patients, the C/I ratio with IMP was below the normal range, indicating crossed cerebellar diaschisis

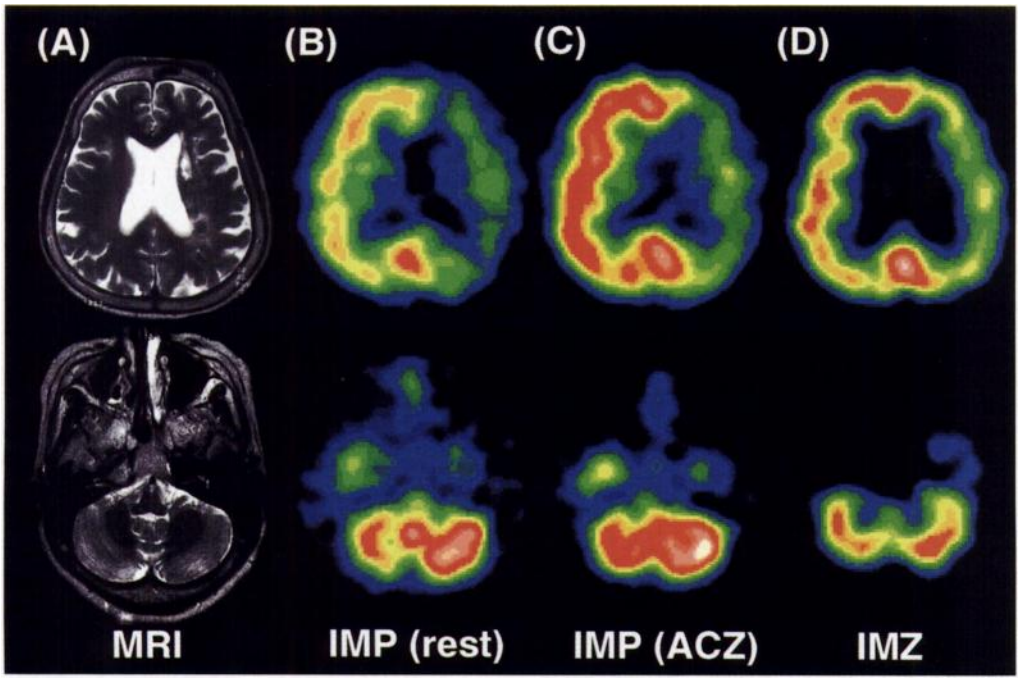

FIGURE 2. (A) MR and (B–D) SPECT images for Patient 9. (A) MRI revealed a subcortical infarction in the left corona radiata, with no involvement of the cortical area. (B) Iodine-123-IMP SPECT in the resting state revealed severe low perfusion in the left MCA territory and right cerebellum. (C) After acetazolamide challenge, markedly decreased perfusion reserve in the left cerebral hemisphere was observed. (D) Iodine-123-iomazenil SPECT revealed moderately low accumulation in the left MCA territory. The asymmetry of uptake in the cerebellum with ^{123}I-iomazenil was less prominent than that with ^{123}I-IMP.

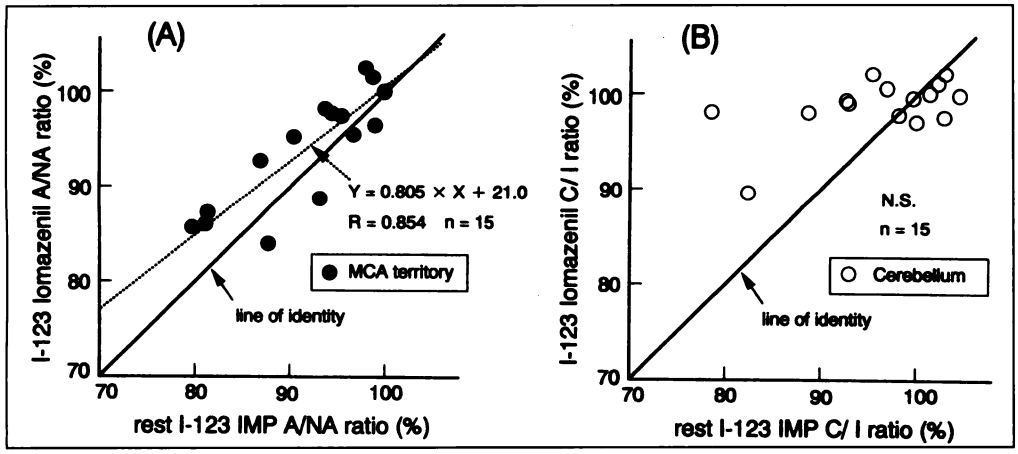

FIGURE 3. Relationship between (A) the count ratio of the affected MCA territory to the nonaffected (A/NA ratio) and (B) the count ratio of the contralateral cerebellar cortex to the ipsilateral cerebellar cortex (C/I ratio) with ^{123}I-iomazenil and ^{123}I-IMP in the resting state.

(*17*). However, the C/I ratio with IMZ was decreased in only one patient, and the degree of decrease was less than that with IMP (Patient 9; Fig. 2).

In Figure 4, the A/NA ratios with IMZ are plotted against the mean absolute rCBF values of the affected MCA territory in the resting state. There was no significant correlation between the A/NA ratio with IMZ and the hemispheric absolute rCBF value.

In Figure 5, the A/NA ratios with IMZ are plotted against the duration of ischemia. Data for all 15 patients did not show a significant time-dependent change of IMZ A/NA ratio. However, in 9 patients without cortical lesions, the IMZ A/NA ratio was significantly inversely correlated with the duration of ischemia ($r = -0.699$; $p < 0.05$). In patients with cortical lesions, there was no significant time-dependent reduction of IMZ A/NA ratio.

Table 2 shows the A/NA ratio with IMZ and %INC of the affected MCA territory. Five patients had a decreased A/NA ratio with IMZ. Of these patients, only 1 had a decreased %INC (Patient 9), and the remaining four patients had a normal %INC. In 2 of the 4 patients with normal %INC (Patients 11 and 15), cerebral hemispheric atrophy was observed on MRI, suggesting the presence of neuronal loss due to chronic ischemia, where duration was 2 yr and 9 yr. Figure 6 shows MRI and SPECT images for a representative patient (Patient 11; IMP A/NA ratio = 87.3%, %INC = 44.5%, IMZ A/NA ratio = 84.5%). The other 2 patients with normal %INC (Patients 2 and 8) did not exhibit hemi-atrophy on MRI, with duration of 1.5 yr and 47 days.

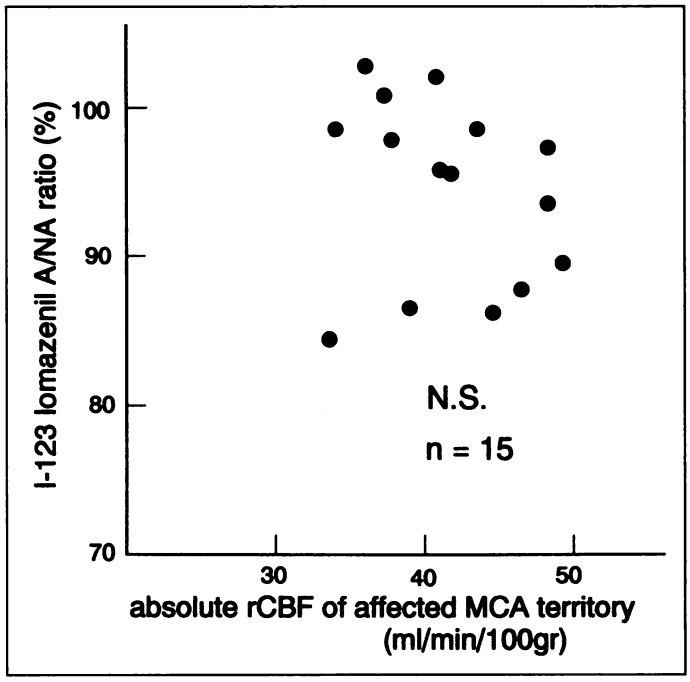

FIGURE 4. Relationship between the hemispheric absolute rCBF on the affected side and the count ratio of the affected MCA territory to the nonaffected (A/NA ratio) with ^{123}I-iomazenil.

DISCUSSION

In this study, we performed IMZ SPECT in patients with thrombotic cerebral ischemia, and compared results with CBF and cerebral perfusion reserve determined using the split-dose IMP SPECT method (*3*). In most patients examined, the distribution of IMZ differed from that of IMP, and the degree of reduction of IMZ uptake in the affected MCA territory was smaller than that of IMP. Odano et al. (*12*) performed a histopathological study in gerbils with chronic infarction using dual tracer of glucose metabolism and IMZ, and reported that when viable neurons with low functional activity remain intact, normal in vivo binding of IMZ with hypometabolism is demonstrated. It also has been reported that neurons in mild ischemic lesions are not damaged morphologically (*18,19*). Preserved IMZ uptake in regions with reduced IMP uptake area might reflect an ischemic threshold above which neurons are viable.

On the other hand, the IMZ and IMP A/NA ratios obtained in this study correlated well. Hatazawa et al. (*13*) reported that

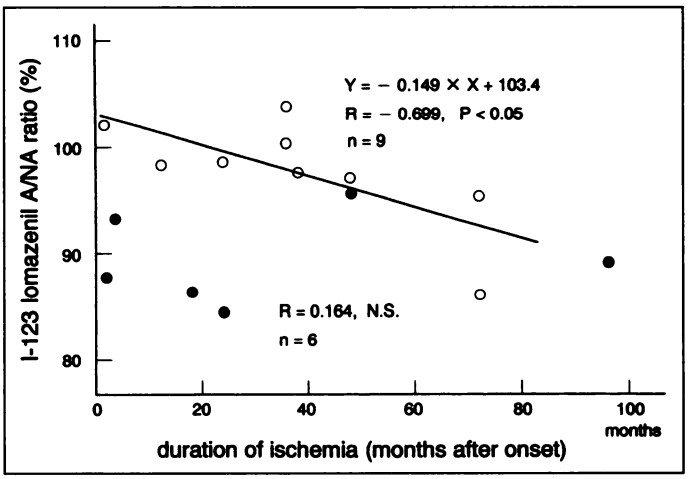

FIGURE 5. Relationship between the duration of ischemia and the count ratio of the affected MCA territory to the nonaffected (A/NA ratio) with ^{123}I-iomazenil. A significant negative correlation ($r = -0.699$; $p < 0.05$) was observed in 9 patients without cortical lesions (○). No significant time-dependent reduction of ^{123}I-iomazenil A/NA ratio was observed in 6 patients with cortical lesions (●).

TABLE 2
Relationship Between Affected/Nonaffected (A/NA) Ratio with Iodine-123-Iomazenil and Perfusion Reserve of Affected Middle Cerebral Artery Territory

	%INC of affected MCA territory	
	<30%	≥30%
IMZ A/NA ratio		
Normal ≥90% <110%	5	5
Decreased <90%	1	4

%INC = percent increase of cerebral blood flow induced by acetazolamide; MCA = middle cerebral artery; A/NA ratio = count ratio of the affected MCA territory to the nonaffected.

reduction of IMZ uptake in the infarct and peri-infarct areas compared with nonaffected hemisphere was of the same degree as for CBF. We excluded infarcted area from ROIs, therefore reduced IMZ binding in the affected MCA territory may have corresponded to incomplete infarction, MRI-negative ischemic damage surrounding an ischemic center (*14,20*).

By experimental model of MCA occlusion in macaque monkeys and rats, the extent of neuronal loss depends on both intensity and duration of ischemia (*21,22*). In this study, however, IMZ uptake did not correlate with absolute rCBF value (Fig. 4). One possible explanation for this is wide physiological fluctuation in absolute rCBF values in clinical situation (*1*). To elucidate the relationship between the severity of ischemia and neuronal viability in clinical cases, further studies and a larger number of studies are needed. On the other hand, in patients without cortical lesions, A/NA ratio with IMZ inversely correlated with the duration of ischemia. This finding suggests that neuronal loss progresses over months, as reported in some experimental studies (*23,24*). In patients with cortical lesions, however, the reduction of IMZ binding did not show a time-dependent change. In these cases, the influence of initial ischemic damage was strong, and the duration of ischemia showed little influence on IMZ binding. Of course, the difficulty of accurate determination of ischemic duration and the small sample size might affect such conflicting results. To clarify the relation of ischemic duration on neuronal damage, serial studies of IMZ binding in individual cases are certainly needed.

As shown in Figure 3B, crossed cerebellar diaschisis (*17*) was found in 5 of 15 patients in this study. However, this was in most cases not associated with reduction of IMZ, which is consistent with the previous reports (*13,14,25*). This finding indicated that alteration of IMZ uptake is not due to altered CBF but may predominantly reflect neuronal damage.

The reduction in IMZ uptake was not directly related to cerebral perfusion reserve as a whole (Table 2). Of 5 patients with a decreased A/NA ratio with IMZ, only 1 had decreased %INC. Hatazawa et al. (*25*) examined 5 patients with subcortical hemorrhage by IMZ and found that those with severely decreased IMZ uptake in the remote cortical area exhibited cortical symptoms. Weiller et al. (*26*) studied strictly subcortical infarcts after MCA occlusion. In many of their patients (26 of the 57 cases studied) symptoms of cortical damage were noted and they speculated that aphasia or neglect after subcortical infarcts are probably due to selective neuronal loss in the cerebral cortex due to prolonged MCA occlusion. Recently, Garcia et al. (*27*) examined MCA occlusion in rats and showed a close correlation between the number of necrotic neurons and the severity of the neurological deficits. In our study, 1 patient (Patient 9) with cortical sign of motor aphasia had only subcortical infarct on MRI, and showed reduced IMZ uptake in the MRI-negative Broca area. These results suggest that alterations in IMZ uptake reflect neurological deficits corresponding to the cortical area.

On the other hand, 4 patients had both decreased A/NA ratio of IMZ and normal %INC. In general, neurons are more vulnerable to reduction of blood flow and oxygen deficiency than either glial cells or blood vessels (*19*). Mies et al. (*28*) observed a decreased number of cortical neurons in the area surrounding experimentally produced chronic infarction in the cat brain. In a transient MCA occlusion model in the rat, Hara et al. (*29*) observed that cerebral hemi-atrophy on the ipsilateral to the affected side develops time-sequentially. In this study, 2 of 4 patients with normal %INC, in whom the ischemic duration

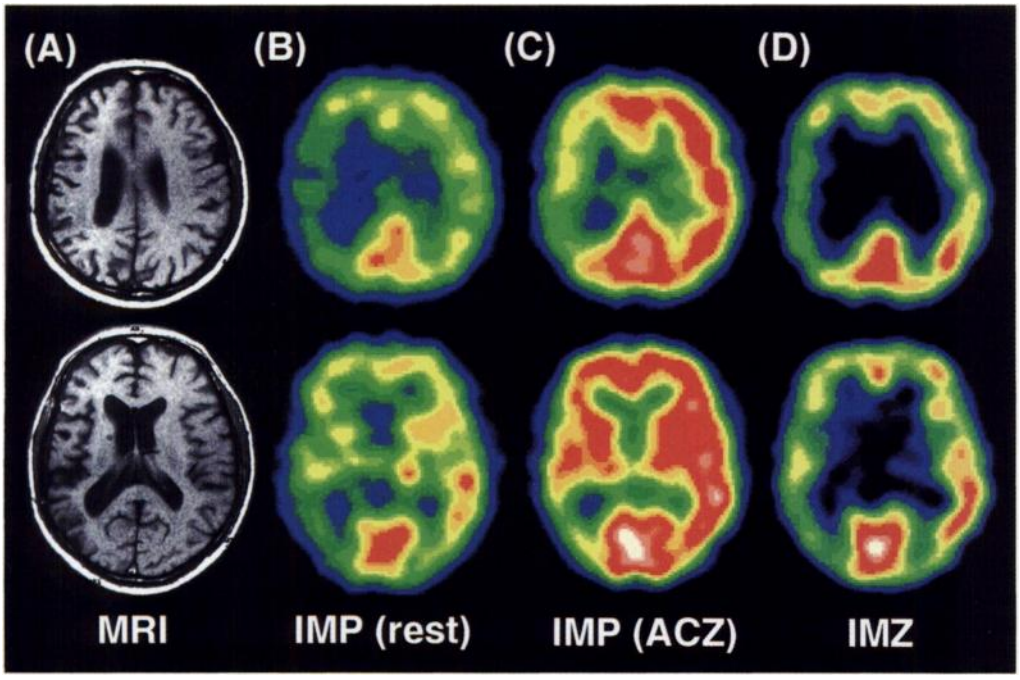

FIGURE 6. (A) MR and (B–D) SPECT images for Patient 11. (A) MRI demonstrated hemispheric atrophy of the right side with cortical infarction in the right temporal lobe. (B) Iodine-123-IMP SPECT in the resting state revealed a perfusion deficit in the infarcted area and low perfusion throughout the entire territory of the MCA. However, after (C) acetazolamide challenge, cerebral perfusion reserve in the right hemisphere was preserved, except in the infarcted area. (D) Iodine-123-iomazenil SPECT revealed low accumulation throughout the entire territory of the MCA on the right side, suggesting the presence of neuronal loss associated with cortical atrophy.

was longer than other two patients, exhibited cerebral hemiatrophy on the affected side. In these cases, neuronal loss associated with cortical atrophy was visualized using IMZ SPECT. The other 2 patients with normal %INC did not exhibit hemi-atrophy on MRI. In these cases, decreased IMZ uptake might also represent ischemic damage of the previous stage of the disease. Although the reason why %INC was normal in these cases is unclear, we speculate two possible mechanisms. First, initially impaired perfusion reserve may improve spontaneously with time due to collateral development (*30,31*). Second, reduced metabolic demand due to ischemia-induced neuronal death, which could not be visualized by MRI, might cause matched perfusion reserve (*1*).

This study includes several methodological limitations. First, we did not perform quantification of benzodiazepine receptor binding using compartment analysis and other recently developed methods (*32,33*). However, Onishi et al. (*34*) reported that the images obtained 3–3.5 hr after injection represent as a relative map of benzodiazepine receptor binding. Accordingly, the IMZ images obtained 180 min postinjection in this study most likely reflect specific binding. Second, we were unable to include an adequate number of normal subjects. Therefore, assessment of the diagnostic value of this new radiopharmaceutical will require study of a greater number of normal individuals and patients with ischemic cerebrovascular disease.

CONCLUSION

IMZ uptake was decreased in severe ischemic lesions with decreased perfusion reserve, and also was decreased in ischemic lesions with preserved perfusion reserve where, in part, cortical atrophy could be observed due to chronic ischemia. IMZ uptake was almost normal in the contralateral hypoperfused cerebellum, indicating that neurons in these areas were functionally deafferentiated. IMZ SPECT provides new information regarding neuronal damage that may not be revealed by other SPECT imaging tracers, and is clinically useful for the evaluation of thrombotic cerebral ischemia.

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