ORIGINAL ARTICLE

Changes in Benzodiazepine Receptor Binding Detected with SPECT in Patients with Cerebral Infarction

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Abstract. SPECT (single photon emission computed tomography) using iomazenil (IMZ) as a ligand for benzodiazepine receptors has recently been developed. Feasibility of the technique for detecting neuronal damage in the cerebral cortex was evaluated in 17 patients with cerebral infarction, specifically, patients with internal carotid artery (ICA) thrombosis (n=6), middle cerebral artery (MCA) thrombosis (n=5) and embolism (n=6). IMZ SPECT was performed 5 to 17 days after stroke. Following the injection of 123I-IMZ 167 or 222 MBq intravenously, images were obtained at 15 minutes (early image) and 180 minutes (late image). In 11 cases, ⁹⁹mTc-HM-PAO (hexamethyl-propylamine oxime) SPECT was also performed to measure cerebral blood flow (CBF). MRI was performed in all cases to elucidate areas of infarct. Early images from IMZ SPECT correlated well with those from HM-PAO, suggesting that early scans using IMZ SPECT reflect mainly CBF. In late images from IMZ SPECT, observed lesions were consistent with infarcted areas on MRI in most cases. However, in 3 cases of ICA thrombosis, 1 case of MCA thrombosis and 1 case of embolism, late IMZ SPECT imaging showed that the affected area was wider than apparent infarcts on MRI, indicating that the cerebral cortex, which was intact on MRI, was also involved. In these patients, clinical signs of cortical involvement were observed as well. These results suggest that moderately reduced CBF may affect cortical neurons without inducing apparent infarct, and such damage can be detected with IMZ SPECT. (Keio J Med 47(3): 168-173 September 1998)

Key words: benzodiazepine, receptor, SPECT, cerebral infarction, iomazenil

Introduction

It is well established that a central type of benzodiazepine receptor is located specifically on neurons, so any reduction in its binding capacity is considered neuronal loss or damage.¹,² With autoradiographic methods or positron emission tomography, changes in the density of benzodiazepine receptors were reported clinically in human patients with degenerative diseases such as Alzheimer’s disease,³ olivopontocerebellar atrophy,⁴ and Friedreich ataxia.⁵ Recently SPECT (single photon emission computed tomography) constructed images of the density and distribution of benzodiazepine receptors have come into clinical use.¹²³I-iomazenil (IMZ) is an analogue of flumazenil and binds specifically to the central type of the benzodiaze-

pine receptor.⁶-⁹ Utilizing this SPECT tracer, clinical studies have already been done for patients with epilepsy¹⁰ and Alzheimer’s disease.¹¹

Stroke is also a subject of interest in the search for possible application of this ligand. Animal experiments have already been reported that show decreased binding to the central type benzodiazepine receptors 2 to 8 days after ischemia.¹² Yet a more precise evaluation of neuronal damage in relation to reduced cerebral blood flow (CBF) and the area of infarct has not been achieved. Moderately reduced CBF might affect the cortical neurons without apparent infarct on CT (computed tomography) or MRI (magnetic resonance image) in either the acute phase¹³,¹⁴ or the chronic phase.¹⁵,¹⁶ Such neuronal damage might be detected by measuring the benzodiazepine receptor density with
IMZ SPECT. Therefore, the feasibility of using this tracer was evaluated in patients in the acute or subacute phase of cerebral infarction.

**Materials and Methods**

Seventeen patients with cerebral infarction in the acute or subacute phase were examined (Table 1). All patients underwent carotid echo and magnetic resonance angiography; based on the imaging examination and clinical data, diagnoses were made as follows: internal carotid artery (ICA) thrombosis (n = 6, age 57.3 ± 12.0 (mean ± SD), 5 males and 1 female), middle cerebral artery (MCA) thrombosis (n = 5, age 57.8 ± 10.7, 2 males and 3 females) and cardiac embolism (n = 6, 60.5 ± 9.5, 4 males and 2 females). To avoid influence of drug intake on measurement of benzodiazepine receptor, it was assured that patients did not take any antianxiety drugs more than one month before SPECT examination for benzodiazepine receptors. All patients gave their informed written consent. Their family substituted for those who could not write with their hand.

SPECT imaging for benzodiazepine receptors was performed at 5 to 17 days after the onset of stroke. The ligand we used was ethyl-5,6-dihydro-7-ido-5-methyl-6-oxo-4H-imidazo[1,5a] [1,4]-benzodiazepine-3-carboxylate (123I-iomazenil) (Mediphysics, Tokyo). Following the injection of 167 or 222 MBq of 123I-iomazenil intravenously, images were taken at 15 minutes (early image) and 180 minutes (late image) using a triple-headed rotating gamma camera GCA9300A/HG (Toshiba, Tokyo).

To compare the images with a conventional SPECT image for CBF, SPECT scanning with 99mTc-HM-PAO (hexamethyl-propylamine oxime) was also performed on each patient on one other occasion.

Brain MRI’s were taken in all cases to elucidate the infarcted area.

**Results**

**ICA thrombosis**

Six patients with ICA thrombosis were studied using IMZ SPECT. Figure 1a shows an early IMZ SPECT image from case 1. The ligand accumulation was diffusely low in the territory of the left ICA. The accumulation was also reduced in the cerebellum on the opposite side. Figure 1b is the HM-PAO image from the same case, also showing the reduced accumulation in the territory of ICA and in the cerebellum on the

**Table 1. Summarized Data of Images**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Age mean ± SD</th>
<th>Sex</th>
<th>Cortical Sign</th>
<th>Early Image c/w HMPAO</th>
<th>Late Image</th>
<th>Cortical Involvement</th>
<th>Cortical Involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>case 1* Thrombosis of ICA</td>
<td>78 F</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes**</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>case 2* Thrombosis of ICA</td>
<td>55 M</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>case 3 Thrombosis of ICA</td>
<td>62 M</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes*</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>case 4 Thrombosis of ICA</td>
<td>43 M</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes*</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>case 5 Thrombosis of ICA</td>
<td>50 M</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>case 6 Thrombosis of ICA</td>
<td>56 M</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>case 7* Thrombosis of MCA</td>
<td>73 F</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes**</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>case 8 Thrombosis of MCA</td>
<td>44 M</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>case 9* Thrombosis of MCA</td>
<td>56 M</td>
<td>No</td>
<td>n.d.</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>case 10 Thrombosis of MCA</td>
<td>54 F</td>
<td>No</td>
<td>n.d.</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>case 11 Thrombosis of MCA</td>
<td>62 F</td>
<td>No</td>
<td>n.d.</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>case 12* Embolism of MCA</td>
<td>53 F</td>
<td>Yes</td>
<td>(No)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>case 13 Embolism of MCA</td>
<td>76 F</td>
<td>Yes</td>
<td>n.d.</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>case 14 Embolism of MCA</td>
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<td>Yes</td>
<td>n.d.</td>
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<td>Yes</td>
</tr>
<tr>
<td>case 15 Embolism of MCA</td>
<td>57 M</td>
<td>Yes</td>
<td>n.d.</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>case 16 Embolism of MCA</td>
<td>66 M</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes**</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>case 17 Embolism of MCA</td>
<td>50 M</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

* Actual pictures are shown in Figs. 1 and 2. c/w HMPAO: compatible with an HMPAO image.

** Late images correlate more with clinical signs than with MRI. (No): the HMPAO image was taken later in the chronic phase.
opposite side, indicating crossed cerebellar diaschisis (CCD). These results are consistent with previous reports describing how early scans using IMZ SPECT mainly reflect CBF. A late image of IMZ in the same patient is shown in Fig. 1c. The tracer accumulation was reduced in the left frontal and parietal cortices, as well as in part of the occipital cortex. Yet on MRI, the infarct was localized to basal ganglia and centrum semiovale, and the cortex was not involved (Fig. 1d). These findings suggest that moderately reduced CBF led to degeneration of cortical neurons and loss of benzodiazepine binding capacity in the field without apparent infarct on MRI. Clinical symptoms of cortical involvement in this patient, such as aphasia, also indicated damage to cortical neurons. Additionally, CCD was not observed in the IMZ SPECT late image, suggesting that neurons in the cerebellum had not degenerated despite decreased CBF in the area. This result is consistent

Fig. 1 Actual images of SPECT and MRI in two cases of ICA thrombosis (case 1 (a–d) and case 2 (e–f)). a; Early image using IMZ SPECT in case 1. Decreased accumulation is seen in the territory of the left ICA. b; HM-PAO SPECT image showing reduced CBF in the left ICA territory in case 1. The pattern is consistent with that of the early image from IMZ SPECT. c; Late IMZ SPECT image in case 1. Decreased accumulation of the tracer is observed diffusely in the affected cortex. d; MRI in case 1. The cerebral cortex is spared. e; Late image of IMZ SPECT in case 2. Accumulation of the ligand is symmetric over both hemispheres. f; MRI in case 2. The infarct is limited to the deep white matter.
with the current idea that reduced CBF in CCD is secondary to hypofunction of cerebellar neurons, instead of neuronal degeneration.

No heterogeneities in IMZ accumulation were found in the late image from case 2, which was another case of ICA thrombosis (Fig. 1e). MRI revealed that the infarct was limited to the deep white matter of the left cerebral hemisphere (Fig. 1f). Clinically, no cortical involvement was apparent. The findings in this case indicate that IMZ accumulation in the late image remains homogeneous when the cortical neurons are intact.

The summarized results from patients with ICA thrombosis are shown in Table 1. Two patients had cortical infarcts and four had infarcts localized in the deep white matter or basal ganglia (Table 1). In all cases, early images showed decreased accumulation of IMZ in the territory of the affected ICA. The patterns of reduction corresponded well with that of HM-PAO, suggesting that the early image from IMZ SPECT mainly reflects CBF. In the late images from IMZ SPECT, cases 4 and 6 showed a localized defect of the tracer consistent with the area of infarct on MRI. In these cases, neurons were considered to be completely destroyed by the infarction, resulting in the loss of benzodiazepine receptor binding capacity. Another case, case 2, showed no cortical involvement either in the late IMZ SPECT images or in MRI, even though CBF was decreased in the territory of the ICA. In this case, reduction of CBF is suggested to have been so mild that cortical neurons could survive without loss of IMZ receptors. In the other three cases, IMZ in the late image was diffusely decreased in the territory of the affected ICA without apparent cortical involvement in the IMZ SPECT late image remains homogeneous when the cortical neurons are intact.

**Emboli**

Six cases of cardiac embolism were studied. MRI in case 12 showed a hemorrhagic infarct in the MCA territory (Fig. 2h). In Fig. 2e, the early scan using IMZ SPECT showed high accumulation of tracer in the area of infarction. Since the early image is thought to reflect CBF mainly, hyperemia after recirculation was suggested. CCD on the opposite side of the infarction was also observed in the image. In this case, HM-PAO SPECT was performed in the chronic phase and could not be compared directly with IMZ SPECT. The HM-PAO SPECT image showed decreased CBF in the infarcted area (Fig. 2f). In the late scan of IMZ SPECT, decreased accumulation was observed in the infarcted area (Fig. 2g).

Five patients (case 12, 13, 14, 15 and 17) had cortical infarction, and in all patients, the IMZ accumulation in the late image was low in the affected cortical area, suggesting necrosis of neurons in the area. The infarct in case 16 was localized in the deep white matter, while the accumulation of IMZ in the late scan was decreased in the cortex adjacent to the infarct. This also may have been due to moderately reduced cortical CBF affecting the neurons without apparent infarct.

**Discussion**

The results of the present study are summarized as follows: (1) In patients with cerebral infarction, early scans using IMZ SPECT mainly reflect CBF. (2) Late images using IMZ SPECT are useful for detecting neuronal degeneration of the cortex, especially when moderately reduced CBF has induced neuronal damage without apparent infarct on MRI. (3) The two rules above can be applied to major artery thrombosis as well as embolism.

The present study did not include any healthy volunteers as controls. According to previous research on healthy controls, the early scan using IMZ SPECT primarily reflects CBF and the late scan represents benzodiazepine binding potential.\(^7\)\(^-\)\(^9\) In late images from these healthy volunteers, accumulation of the ligand was observed mainly in the cerebral cortex, while basal ganglia and the cerebellum lacked accumulation. This finding reflects the fact that benzodiazepine receptors are mainly expressed on cortical neurons. In the present study, the same pattern of accumulation was observed in patients with infarction.

Three cases of ICA thrombosis, one case of MCA thrombosis and one case of MCA embolism showed
Fig. 2 Representative images of SPECT and MRI in two cases of MCA thrombosis (case 7 (a–b) and case 9 (c–d)) and a case of MCA embolism (case 12 (e–h)). a; Early IMZ SPECT image in case 7. Accumulation of IMZ is decreased in the territory of the right MCA, suggesting hypoperfusion. b; Late IMZ SPECT image in case 7. The reduced accumulation of IMZ persists in the late image. c; Late image using IMZ SPECT in case 9, showing an intact pattern of accumulation. d; MRI in case 9. Lacunar infarcts are observed. e; Early IMZ SPECT image in case 12, showing hyperperfusion in the affected area. f; HM-PAO image in case 12 showing hypoperfusion in the chronic phase. g; Late IMZ SPECT scan in case 12. Reduced accumulation is observed in the affected cortex. h; MRI in case 12. Hemorrhagic infarct is seen.
low accumulation of IMZ in late images without apparent infarct in the cortex on MRI. Furthermore, these findings were accompanied by cortical signs. As for the mechanism of these findings, moderately reduced CBF is thought to induce neuronal degeneration in the cerebral cortex without distinct necrosis, an idea that suggests the name “incomplete infarction”.

A similar process has been proposed by Nakagawara and Garcia, who used IMZ SPECT and by Matsuda, who used autoradiography. Some of these researchers employed only animal models of infarction and some of them studied a limited number of patients without doing complete assessments, for example, of clinical symptoms, MRI findings and CBF measurements. The present study is the first that clearly provides the evidence of incomplete infarction by comparing different patterns of CBF reduction in many cases, in addition to the clinical signs and MRI findings.

Aside from the usefulness in the assessment of organic damage in neurons, benzodiazepine receptor SPECT may also be useful for the assessment of specific changes of the receptor itself. For instance, patients suffering from anxiety disorder or chronic intoxication by antianxiety drugs might carry altered density of benzodiazepine receptors. Further studies are needed for such possible usage.

In conclusion, moderately reduced CBF can result in neuronal damage without distinct infarct on MRI, and the IMZ SPECT is useful in detecting such neuronal damage in the cerebral cortex.

References


