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Introduction

Nimodipine (BAY e 9736) is a dihydropyridine type calcium antagonist first synthesized at Bayer A. G. Its structural formula is shown in Figure 1. The reported pharmacologic actions of this agent based on animal studies are cerebral vessel-selective vasodilating action[1)], cerebral blood flow increasing actioin[1-4)], cerebral circulatory disturbance improving action[5)], cerebral circulatory disturbance improving action[1,6)] and cerebral vasconstriction inhibiting action[7-10)]. In addition, platelet aggregatin inhibiting and erythrocyte deformability promoting actions in humans have also been reported[11)].

Regarding the influences of nimodipine on brain circulation and metabolism, many findings including increases in local cerebral blood flow (LCBF) and regional cerebral glycolysis turnover have been generated by many preclinical studies.[1-4)] Meanwhile, the ^{133}Xe clearance method is the routine method for determination of cerebral blood flow that is used clinically today.[12,13)] However, this method does not yield information more than an approximation of the blood flow in the brain surface and does not provide even a clue to the blood flow at the lesion underneath the cerebral cortex and in its neighborhood. Such being the situation, positron emission tomography (PET) characteristically provides information on blood flow, in the form of a quantitative tomographic image, within the brain including the local lesion. Furthermore, this technique is expected to become the most reliable quantitative method ever available, although at this moment we do not know of a report, whether domestic or foreign, that has been addressed to a procedure for clinical evaluation of drug efficacy utilizing this technique.

In view of the above situation, we investigated changes in LCBF after administration of nimodipine by the $C^{15}O_2$ inhalation method utilizing the PET (ECATII, ORTEC) installed in our university.

Subjects

The study was conducted in 2 patients with ischemic cerebrovascular disorder (1 with cerebral infarction and 1 with subclavian steal syndrome) who were examined at the Cyclotron Radioisotope Center, Tohoku University 1985. Incidentally, neither of the patients had received Ca antagonists.

Method

The LCBF was determined by sustained inhalation of $C^{15}O_2$ [14,15] . The measurment was performed before and after single oral administration of nimodipine 30 mg.

Results

Case 1 T. T. aged 67, male

Diagnosis: Cerebral infarction

Past history: Hypertension was pointed out in 1960.

Present illness: In December 1984, right hemiplegia appeared. The patient was diagnosed as having cerebral infraction and admitted to the department of neurology of our hospital. Neurologically, right hemiplegia and mild speech disorder were found. CT showed low-density areas in the region of the left middle cerebral artery.

On March 12, 1985, PET was performed and LCBF was measured immediately before and 90 minutes after administration of nimodipine, 30 mg p.o. The section for measurement was 40 mm above the OM line (Fig. 3). LCBF before nimodipine administration showed a remarkable decrease on the infarcted side and the normal lower limit on the non-infarcted side, as shown in Fig. 3. After nimodipine administration, LCBF increased to about 5 times as high as the pre-administration value (2.8→14.5 ml/100 g·min). On the non-infarcted side, no difference was found before and after nimodipine administration.

Case 2 Y. K., aged 56, male

Diagnosis: Subclavian steal syndrome

Past history: Nothing paticular

Present illness: In January, 1980, the patient suddenly lost consciousness when he sat up at night. In 1982, a floating sensation of the body appeared. On October 25, 1984, vertigo and epicardial lanxiety appeared. On neurological examination, bruits were heard (R>L), and right-left difference in blood pressure in upper limbs (R>L) and decreased superficial sensation in the distal ends of the upper and lower limbs were found. Angiography revealed a narrowing of the origin of the right vertebral artery. On right vertebral arteriography, the left vertebral artery was retrogradely delineated .

On April 23, 1985, PET was performed and LCBF ws measured immediately before and 45 minutes after administration of nimodipine, 30 mg p.o. The section for measurment was 40 mm above the OM line (Fig. 4). As shown in Fig. 5, LCBF before nimodipine administration was relatively high at 82 ml/100g min in the right middle cerebral artery but was normal in the left middle

cerebral artery, posterior cerebral artery, etc. After nimodipine administration, LCBF tended to increase in all the above-mentioned regions, and particularly in the middle cerebral artery, the increase was approximately 30 %.

Discussion

In the case of cerebral infarction in the choronic stage (Case 1), the cerebral region showing a marked decrease in LCBF was the infarcted region with a chronic need for blood, and it is interesting to note that the administration of nimodipine produced an approximately 5-fold increase in LCBF, from 2.8 ml/100g·min. to 14.5 ml/100 g·min., selectively in this region, for this result seems to be a piece of objective evidence that this drug produces cerebral circulation improving effects in patients with cerebral infarction in the chronic stage. Furthermore, the fact that nimodipine had little influences on LCBF at the non-infarcted side suggests that this drug tends to act predominantly on the affected side in cerebrovascular disturbances.

In Case 2, the brain (particularly the brain system) seemed to have been made olygemic transiently or continually due to a circulation abnormality associated with a vascular lesion. The finding in this case that the administration of nimodipine caused a significant increase, of about 30 %, in the whole-brain mean LCBF value suggests, as the mechanism of action, the co-existence and interplay of two factors, an improvement in blood flow in the stolen basilar artery region and an increased blood flow in the carotid artery region. The above result suggests the LCBF-increasing action of nimodipine. The substantially normal LCBF value before drug administration in this case may be accounted for by the fact that the patient was in an in-between period between attacks and had been put in good rest prior to the examination.

The results of our study in the above two cases of PET suggest that nimodipine has a LCBF-increasing action and, in diseases involving local lesions such as cerebral infarction, may produce a region-specific flow-increasing effect.

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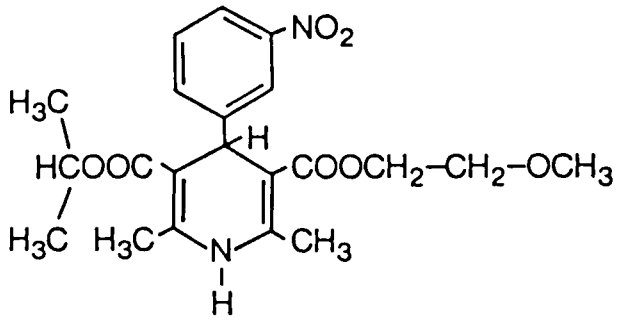

Chemical name : isopropyl 2-methoxyethyl 1,4-dihydro-2,6-dimethyl-4-(m-nitrophenyl)-3,5-pyridine dicarboxylate

Fig. 1. Chemical structure and chemical name of nimodipine

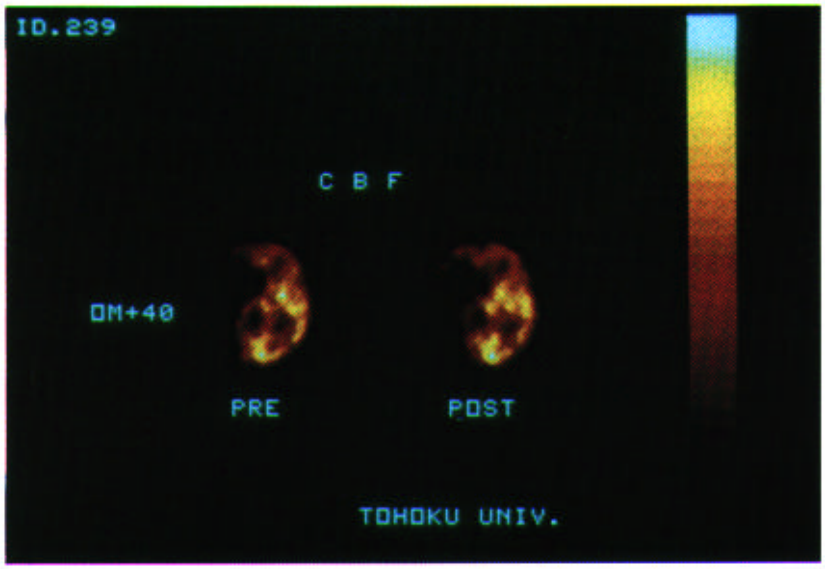

Fig. 2. The PET on the section 40 mm above the OM line in a patient in the Choronic stage of cerebral infarction.
T. T. A 67-year-old man. A case of cerebral infarction in the chronic stage about 4 month after onset in whom CT showed low-density areas in the region of the left middle cerebral artery.
Left: The PET 90 minutes after administration of nimodipine, 30 mg p.o.

	Before nimodipine administration	After administration of nimodipine
Infarcted side (A)	2.8	14.5
Non-infarcted side (B)	34.7	36.2

Unit : ml/100g·min
Normal value : 40-60ml/100g·min
Section for measurement : 40mm above the OM line

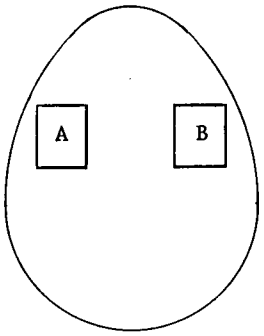

Fig. 3. Values of LCBF and sites of LCBF measurement in a patient with cerebral infarction in the chronic stage

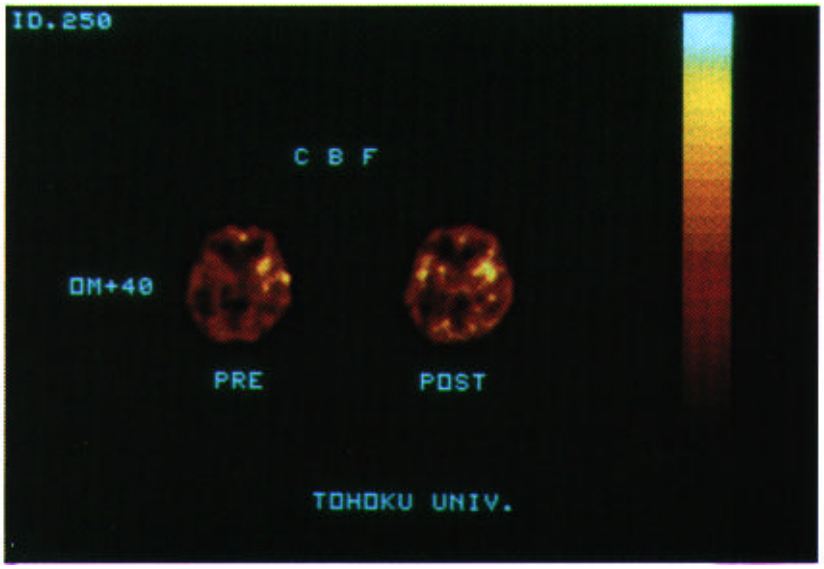

Fig. 4. The PET on the section 40 mm above the OM line in a patient with subclavian steal syndrome.
Y. K. A 56-Year-old man. A case of subclalvian steal syndrome in which angiography showed a narrowing of the origin of the right vertebral artery and right vertebral arteriography showed retrogradeness of the left vertebral artery.
Left: The PET before nimodipine administration.
Right: The PET 45 minutes after administration of nimodipine, 30 mg p.o.

	Before nimodipine administration	After administration of nimodipine
Left middle cerebral artery region (A)	64	85
Right middle cerebral artery region (A')	82	102
Posterior cerebral artery region (B)	59	67

Unit : ml/100g min
Normal value : 40-60ml/100g min
Section for measurement : 40mm above the OM line

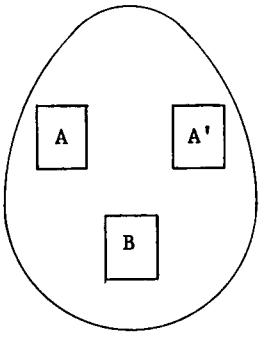

Fig. 5. Values of LCBF and sites of LCBF measurement in a patient with subclavian steal syndrome