Effects of Co-Dergocrine Mesylate (Hydergine®) in Multi-Infarct Dementia as Evaluated by Positron Emission Tomography

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NAGASAWA, H., KOGURE, K., KAWASHIMA, K., IDO, T., ITOH, M. and HATAZAWA, J. *Effects of Co-Dergocrine Mesylate (Hydergine®) in Multi-Infarct Dementia as Evaluated by Positron Emission Tomography.* Tohoku J. Exp. Med., 1990, **162** (3), 225-233 — Three female patients aged from 74 to 79 with multi-infarct dementia were studied using positron emission tomography (PET) to assess the effect of co-dergocrine mesylate (Hydergine®) on cerebral glucose metabolism. The cerebral glucose utilization (CMRGlc) of each patient was evaluated by PET scan using 2-deoxy- ^{18}F -2-fluoro-D-glucose (FDG). Following the first PET study, 0.04 mg/kg of co-dergocrine mesylate was injected intravenously with 250 ml saline solution, and then the second PET study was performed. The CMRGlc was determined from the images of the PET scan and the radioactivity of ^{18}F in the plasma. After the administration of co-dergocrine mesylate, the value of CMRGlc increased significantly in the cerebral cortex ($p < 0.01$ and $p < 0.05$) and basal ganglia ($p < 0.05$) compared with values before the administration, but no significant increase was found in the centrum semiovale. These results suggest that co-dergocrine mesylate stimulates glucose metabolism of neurons in the human brain. ——— co-dergocrine mesylate; cerebral glucose metabolism; positron emission tomography; dementia; stroke

The investigation of the human brain function has been advanced by measuring a wide variety of functional parameters in vivo on a regional basis in the brain with positron emission tomography (PET) including blood flow, metabolism, pharmacokinetics, tissue pH, and the distribution of chemotherapeutic agents (Phelps et al. 1982; Raichle 1983; Yamamoto et al. 1984). The advantage of this imaging method is that it is not only qualitative, but quantitative, and repeated evaluations are possible. Thus, this study is applicable not

Received September 18, 1990; revision accepted for publication October 17, 1990.

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only to simple diagnosis, but as an index of cerebral metabolism in the pharmacological evaluation of new drugs. It is also possible to evaluate the effect of drugs on cerebral blood flow or metabolism in patients by using PET. The test-retest method by the repeated studies using PET for short period has been established (Brooks et al. 1987).

Glucose is the main substrate for cerebral metabolism and most of the glucose extracted by the brain is oxidized (Sokoloff 1972; Siesjö 1978). Cerebral glucose utilization in certain areas of the brain has been studied with respect to physiological manipulations, such as visual stimulation (Toga and Collins 1981), and various pharmacological treatments (Dow-Edwards et al. 1981; Palacios et al. 1982). Many studies have confirmed a correlation between physiological function and glucose metabolism in the central nervous system (Sokoloff 1977). Therefore, measurements of cerebral glucose utilization can provide an index of brain functions.

Co-dergocrine mesylate (Hydergine®) has been employed in the clinical treatment of senile dementia and cerebral vascular disorders for many years, and its efficacy has been well documented (van Loveren-Huyben et al. 1984; Singer et al. 1985; Thienhaus et al. 1987). In Japan, co-dergocrine mesylate has been in use for the past 27 years. First approved by the FDA in 1981, it is the only drug to be found effective in the treatment of 14 symptoms caused by decrease in mental activity (Yesavage et al. 1981a, b). The purpose of the present study is to determine the immediate influence of co-dergocrine mesylate administration on cerebral glucose metabolism in clinical cases by using PET.

MATERIALS AND METHODS

Three female patients, aged from 74 to 79 years old, with cerebral vascular disease were studied at the Cyclotron and Radioisotope Center, Tohoku University. All patients was diagnosed by clinical examination and psychological tests as well as computed tomography. They exhibited mild left hemiparesis and moderate degree of dementia. The degree of dementia was classified as subnormal or predementia according to Japanese intelligence scale test formulated by Hasegawa, which is similar to the Mini-Mental State Test (Folstein et al. 1975). The Japanese intelligence scale test is consisted of 11 items including verbal and sequence memory, digit span forward, calculation, and visual reaction. Profiles of these three clinical cases are shown in Table 1.

Case 1. A 74-year-old woman, who had suffered mild left hemiparesis and memory disturbance with a lack of insight for 6 months. She was classified as predementia according to the Japanese intelligence scale. Multiple lacunar infarction was revealed by x-ray CT scan.

Case 2. A 79-year-old woman, who had suffered left hemiparesis and memory disturbance for 2 years. She also had calculation disturbance. She was classified as subnormal according to the Japanese intelligence scale. Multiple lacunar infarction was revealed by x-ray CT scan.

Case 3. A 75-year-old woman, who had suffered left hemiparesis and numbness for 4 years. She also had amnesia and nocturnal confusion, and these symptoms were seen to be worsening. She was classified as predementia according to the Japanese intelligence scale. Right prefrontal infarction was revealed by x-ray CT scan.

TABLE 1. *Profiles of three clinical cases*

Case	Age (years)	Sex	Duration	Symptoms and CT scan	Dementia score ^a (point/full mark)
1	74	F	6 M	Left-sided muscle weakness, memory disturbance with lack of insight, apathy. (x-ray CT) multiple lacunar infarction	13.5 32.5
2	79	F	2 Y	Left-sided muscle weakness, memory and calculation disturbance. (x-ray CT) multiple lacunar infarction	22.5 32.5
3	75	F	4 Y	Left-sided muscle weakness and numbness, stepwise deterioration, amnesia, nocturnal confusion. (x-ray CT) right-sided pre-frontal infarction	18.0 32.5

^aDementia score by the Japanese intelligent scale test was divided as follows: 0-10.0, dementia; 10.5-21.5, predementia; 22.0-30.5, subnormal; and 31.0-32.5, normal. F, female; M, months; Y, years.

These three patients were scanned on the PET scanner using the FDG method (Phelps et al. 1979; Reivich et al. 1979) before and after intravenous administration of co-dergocrine mesylate. During the PET studies, the physiological factors were measured, as summarized in Table 2. The subjects' informed consent was obtained before the study. The subjects were scanned with the single-plane ECAT II using a medium-resolution shadow shield to give a resolution of 15 mm in the tomographic plane and an axial resolution of 18 mm (full width at half maximum). A cross of light was projected onto marks on the subjects' heads from three dimensions and their heads were set at the standard points of 30 and 70 mm above and parallel to the orbitomeatal (OM) line (Hatazawa et al. 1988). Before scanning, a short 21-gauge cannula was inserted to a brachial or radial artery for arterial blood sampling. All the procedures were performed in the semidarkened room. The subjects' eyes were closed. At the first PET study, 1.22-1.35 mCi/50 kg of ¹⁸F DG was injected into an arm vein. Cerebral glucose metabolism was measured at 30, 50 and 70 mm above and parallel to the OM line. After the first PET study, co-dergocrine mesylate (0.04 mg/kg) was administrated by intravenous drip infusion with 250 ml saline solution for approximately 30 min. Subjects' heads were repositioned according to the standard points

TABLE 2. *Physiological parameters of the PET studies*

	Before injection	After injection
MABP (mmHg)	115 ± 6	113 ± 7
Blood glucose (mg/100 ml)	108 ± 4	104 ± 6
pH	7.42 ± 0.02	7.42 ± 0.03
PaO ₂ (mmHg)	82.9 ± 2.5	83.3 ± 3.8
PaCO ₂ (mmHg)	38.2 ± 1.1	36.8 ± 1.8

Values are given in terms of mean ± S.D.
Three clinical cases.

using a cross light projected onto their heads as same as the first PET study. After administration of co-dergocrine mesylate, the second PET study was performed by using 6.20-6.40 mCi/50 kg of ^{18}F FDG as well as the first PET study. During each PET study, arterial blood samplings were taken at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 7.5, 10, 15, 20, 25, 30, 40, 50 and 60 min after the intravenous administration of ^{18}F FDG and at the end of the scanning. These blood samples were centrifuged, and the arterial plasma radioactivity of ^{18}F FDG was measured with the cross-calibrated well counter. The arterial plasma glucose concentration of samples taken every 10 min was estimated. CMRGlc was calculated based on the Sokoloff model (Sokoloff et al. 1977; Brooks 1982), using the kinetic rate constants of FDG for gray and white matter determined by Phelps et al. (1979) and a lumped constant (LC) of 0.52 measured by Reivich et al. (1985). Before the emission scanning, a transmission scan using a ^{68}Ge - ^{68}Ga external ring source was performed. The emission data were corrected for attenuation using transmission data.

TABLE 3. *CMRGlc values in each structure before and after the administration of co-dergocrine mesylate*

	Test	Retest
Frontal cortex		
case 1	4.30	5.68
case 2	4.70	5.64
case 3	5.40	5.90
mean $\pm$ s.d.	4.80 ± 0.55	$5.74 \pm 0.14^{**}$
Temporal cortex		
case 1	4.78	5.29
case 2	4.73	5.74
case 3	5.80	6.37
mean $\pm$ s.d.	5.10 ± 0.60	$5.80 \pm 0.54^*$
Occipital cortex		
case 1	4.15	4.70
case 2	5.35	6.62
case 3	6.07	6.50
mean $\pm$ s.d.	5.32 ± 0.92	$5.94 \pm 1.07^*$
Basal ganglia		
case 1	3.72	4.42
case 2	3.89	5.29
case 3	5.73	6.33
mean $\pm$ s.d.	4.49 ± 1.11	$5.35 \pm 0.95^*$
Centrum semiovale		
case 1	3.04	3.44
case 2	3.06	3.71
case 3	3.57	3.63
mean $\pm$ s.d.	3.22 ± 0.30	3.59 ± 0.13

Values are given in mg/100 g/min. Three clinical cases.

* $p < 0.05$, ** $p < 0.01$ compared with values by using a paired t -test between test and retest.

Regional measurements of CMRGlc were made by reading the numerical computer printout of the functional data calculated with appropriate model parameters. Using ^{18}F FDG images, 2.7 cm^2 square regions of interest were put on frontal, temporal and occipital cortex, basal ganglia, and centrum semiovale. Six regions of interest were obtained in each structure from the corresponding anatomical levels of images for each hemisphere. The mean values of 12 regions of interest in the frontal, temporal, and occipital cortex, basal ganglia, and centrum semiovale (six for each hemisphere) were calculated in each study before and after administration of co-dergocrine mesylate. The value of CMRGlc of each PET study was calculated by the half-life correction of ^{18}F radioactivity according to the method developed by Brooks et al. (1987), and the data were analyzed using a paired t -test, with $p < 0.01$ and $p < 0.05$ considered statistically significant.

RESULTS

No significant difference was observed in physiological parameters, including mean arterial blood pressure (MABP), blood glucose, pH, arterial oxygen tension (PaO_2), and arterial carbon dioxide tension (PaCO_2) before and after intravenous drip infusion of co-dergocrine mesylate (Table 2). The cerebral metabolic rate of glucose in each structure of a test and a retest in each case is shown in Table 3. After the administration of co-dergocrine mesylate, the values of CMRGlc increased significantly in the cerebral cortex ($p < 0.01$ and 0.05) and basal ganglia ($p < 0.05$) compared with CMRGlc values before administration, but no significant increase was recognized in the white matter, especially in the centrum semiovale. The rate of increase was approximately 10 to 16%, and this value was above the systematic error of the PET study.

DISCUSSION

An increase in glucose uptake due to prolonged treatment with co-dergocrine mesylate has been reported in animal experiments as well (London and Walovitch 1985; Meier-Ruge 1986). The increase in glucose uptake was observed in many subcortical regions, but no significant increase in glucose uptake was observed in the cerebral cortex. Most cortical areas showed no significant drug effect. However, co-dergocrine mesylate caused a reduction in glucose utilization in the frontal cortex (London and Walovitch 1985). The effect of co-dergocrine mesylate on glucose metabolism was thought to have some relation to certain kinds of neurotransmitters in another animal experiment (Meier-Ruge 1986). On the other hand, long-term administration of co-dergocrine mesylate is known to counteract the age-associated decline in hexokinase and to increase lactate dehydrogenase as seen in homogenates of rat forebrain tissue (Djuricic and Mrsulja 1980). This finding suggests that co-dergocrine mesylate may increase the capacity for cerebral glucose oxidation. Therefore, it has been thought useful to determine whether co-dergocrine mesylate could enhance cerebral glucose utilization in vivo as well (London and Walovitch 1985). There are discrepancies between animal and human studies regarding the effect of co-dergocrine mesylate on regional glucose metabolism. Furthermore, both animal and human studies

have been performed using new imaging methods, such as the autoradiogram and PET study. The present study is limited in that CMRGlc was only determined immediately after the intravenous administration of co-dergocrine mesylate. An acute effect of the drug on CMRGlc was observed. But there remains a need to investigate the effect of co-dergocrine mesylate on CMRGlc by means of prolonged treatment in human studies.

Our research group previously reported the ability of co-dergocrine mesylate to strongly inhibit necrosis of hippocampal pyramidal cells induced by occlusion of bilateral carotid arteries in Mongolian gerbils (Izumiya and Kogure 1988). Biochemical investigations of co-dergocrine mesylate have also revealed its potent actions on some kinds of neurotransmitter receptors (Loew et al. 1979; Ogawa et al. 1987). For instance, co-dergocrine mesylate increases evoked noradrenaline release by simultaneously blocking presynaptic adrenergic autoreceptors and postsynaptic adrenoceptors. Furthermore, according to other studies, co-dergocrine mesylate acts not only as an agonist and an antagonist on the presynaptic and postsynaptic dopamine receptors but on serotonin sensitive receptors (Jaggi and Loew 1976; Markstein 1985).

During ischemia, a great quantity of neurotransmitters such as noradrenaline, glutamate and dopamine are released pathologically from axon terminals (Kogure et al. 1975; Lavyne et al. 1975; Benvenist et al. 1984). This pathologically enhanced release of excitatory neurotransmitters increases the activity of calcium channels in hippocampal neurons and promotes calcium influx (Yanagihara and McCall 1982; Deshpande et al. 1987). Co-dergocrine mesylate is known to have antinoradrenergic effects, thus preventing neurons from transsynaptic overactivity in the adrenergic system induced by ischemic insult. There may be a need to deal with this factor in the prevention of delayed neuronal death in the hippocampus, but its mechanisms are still controversial.

Although the both mechanisms, the increase of glucose uptake in the cortex and the prevention of ischemia induced delayed neuronal death are not identical, it should be emphasized that co-dergocrine mesylate improved neuronal function and had beneficial pharmacological effects on ischemic brain damages.

There was significant depression in the mean cerebral blood flow and cerebral metabolic rate for glucose values in Alzheimer and multi-infarct patients using PET (Dastur 1985; Deutsch and Tweedy 1987). Regional cerebral glucose metabolism was acknowledged as an index of neuronal activity, and the cortical involvement of glucose metabolism was considered to be consistent with the major clinical features of Alzheimer's disease (Foster et al. 1984). In the present clinical study, co-dergocrine mesylate has been shown to increase glucose metabolism of the cortex in the initial stages of vascular dementia patients.

A special research group for Alzheimer's disease in the Department of Health and Human Services of the United States has reported the effectiveness of co-dergocrine mesylate in the treatment of some types of Alzheimer's disease. The

positive clinical effects of co-dergocrine mesylate on dementia have been recognized as justification for its long use and favorable reputation.

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