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Regional cerebral blood flow in Alzheimer's disease: Comparison between short and long-term donepezil therapy

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Objective: Treatment with donepezil improves cognitive function of patients with Alzheimer's disease (AD) when compared to a placebo-controlled group. The purpose of this study was to investigate changes in regional cerebral blood flow (rCBF) of AD patients in short-term and long-term treatment with donepezil. ***Methods:*** rCBF was measured by *N*-isopropyl-*p*-^{123}I-iodoamphetamine (IMP) autoradiography method. CBF measurements were performed in 17 AD patients before treatment and after 3 months (short-term therapy) and 1 year (long-term therapy). Regions of interest were set at cerebral cortex and cerebellar hemisphere. We used absolute CBF and relative CBF expressed as ratio to cerebellar CBF. ***Results:*** Significant increases in relative rCBF were noted in the frontal, parietal and temporal lobes at the end of short-term therapy. rCBF was decreased after the long-term therapy, whereas rCBF was still increased to a slight extent, as compared with the pre-treatment levels. Absolute rCBF showed minimal change and a tendency to decline. ***Conclusion:*** Relative rCBF significantly increased in the short-term donepezil therapy, while following the long-term therapy, rCBF decreased to the pre-treatment level.

Key words: donepezil, Alzheimer's disease, cerebral blood flow

INTRODUCTION

DONEPEZIL HYDROCHLORIDE is an acetylcholinesterase (AChE) inhibitor and is used as a therapeutic agent for Alzheimer's disease (AD). Intracerebral acetylcholine receptors are distributed throughout the brain, and donepezil influences both the pre- and the postsynaptic AChE-positive structures in the human central nervous systems.[1] AChE inhibitors improve the behavioral and attentional symptoms of AD.[2]

In a mass study comparing it with a placebo group, significant improvement in core symptoms, such as impaired cognitive function, was observed after administration for 12–24 weeks.[3] Despite continued treatment with donepezil, the symptoms subsequently progressed, and by one year they had returned to the same degree of severity as at the start of administration; however, the patients' condition was maintained significantly better than that in the untreated group. Some authors have reported evaluation of CBF after short-term AChE inhibitor therapy or one year of administration of donepezil,[4,5] but no reports have included changes in CBF after short-term and long-term administration. In the present study we administered donepezil to Alzheimer's patients and evaluated changes in CBF at 3 months and after long-term administration.

SUBJECTS AND METHODS

Subjects

We investigated 17 patients diagnosed as having Alzheimer's disease according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV),[6] and the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association

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Table 1 Absolute CBF and relative CBF after short-term and long-term therapy

	Absolute CBF (ml/100 g/min)			Relative CBF		
	Baseline	3 months	1 year	Baseline	3 months	1 year
Right superior frontal cortex	35.4 ± 7.3	35.1 ± 5.7	33.9 ± 6.8	0.746 ± 0.068	0.797 ± 0.132*	0.765 ± 0.109
Left superior frontal cortex	36.1 ± 7.0	35.2 ± 5.5	34.3 ± 6.4	0.762 ± 0.070	0.797 ± 0.117	0.779 ± 0.133
Right inferior frontal cortex	36.6 ± 7.5	36.3 ± 5.3	34.6 ± 5.7	0.775 ± 0.107	0.835 ± 0.206	0.790 ± 0.151
Left inferior frontal cortex	35.3 ± 7.2	35.7 ± 5.8	34.3 ± 5.3	0.748 ± 0.106	0.814 ± 0.180*	0.788 ± 0.173
Right motor cortex	42.8 ± 8.0	42.5 ± 7.8	39.0 ± 6.4	0.913 ± 0.130	0.963 ± 0.166	0.890 ± 0.167
Left motor cortex	40.7 ± 6.1	42.8 ± 8.0	38.9 ± 6.2	0.871 ± 0.096	0.967 ± 0.149*	0.888 ± 0.166**
Right parietal cortex	31.9 ± 8.8	31.3 ± 7.0	30.3 ± 8.2	0.667 ± 0.106	0.704 ± 0.128	0.673 ± 0.100
Left parietal cortex	30.5 ± 7.8	31.3 ± 6.2	29.8 ± 8.3	0.640 ± 0.087	0.703 ± 0.094*	0.662 ± 0.113**
Right anterior temporal cortex	36.6 ± 9.8	35.8 ± 7.4	34.5 ± 9.7	0.768 ± 0.130	0.816 ± 0.189	0.771 ± 0.144
Left anterior temporal cortex	35.9 ± 7.9	35.1 ± 6.6	33.7 ± 9.1	0.759 ± 0.096	0.796 ± 0.139	0.757 ± 0.150
Right posterior temporal cortex	37.0 ± 8.2	34.8 ± 5.3	36.1 ± 9.5	0.781 ± 0.118	0.793 ± 0.145	0.802 ± 0.120
Left posterior temporal cortex	35.4 ± 8.0	33.6 ± 5.3	33.6 ± 8.4	0.745 ± 0.096	0.760 ± 0.104	0.748 ± 0.112
mCBF	36.2 ± 7.0	35.8 ± 4.9	34.4 ± 6.5	0.765 ± 0.059	0.812 ± 0.115*	0.776 ± 0.095**
Cerebellum	47.5 ± 9.4	44.7 ± 7.7	45.0 ± 9.7	—	—	—
MMS	21.2 ± 4.9	22.5 ± 3.5	20.7 ± 4.0	—	—	—

* $p < 0.05$ in comparison to baseline CBF
** $p < 0.05$ in comparison of three groups

diagnostic criteria.[7] The patients ranged in age from 49 to 84 y, with a mean age ± SD of 73 ± 9 y. The mean Mini-Mental State Examination (MMSE) score was 21.2 ± 4.9. We measured the CBF of all patients prior to the donepezil therapy. The patients were started at 3 or 5 mg/day of orally administered donepezil for 2 weeks, and received chronic oral dosage (5 mg/day) for over 12 months. The measurement of CBF was repeated in all patients at 3 months of treatment (short-term therapy) and 1 year (long-term therapy) and all subjects gave informed consent to participate.

Method

The measurement of CBF was performed in accordance with the autoradiography method previously reported by Iida.[8] With the subjects at rest in a sitting position with eyes open, 185 MBq of *N*-isopropyl-*p*-^{123}I-iodoamphetamine (IMP) (Nihon Medi-Physics, Hyogo, Japan) was injected intravenously over 1 minute via a cubital vein, and blood specimens were collected 10 minutes later from the contralateral brachial artery. Exactly 1 m*l* of the blood sample was collected with a pipette, and whole blood radioactivity was measured with a well counter (Cobra, Packard Instrument, Meriden, USA). SPECT was begun 22 minutes after the start of the intravenous injection and conducted for 16 minutes using a triple-head SPE system (PRISM IRIX, Picker International, Cleveland, USA) equipped with low-energy parallel collimators. The SPECT images with a matrix of 128 × 128 were reconstructed using ordered-subset expectation maximization (OSEM) reconstructions with 4 iterations and 12 subsets. Attenuation correction was performed using Chang's method and scatter was corrected with triple-energy window techniques.[9]

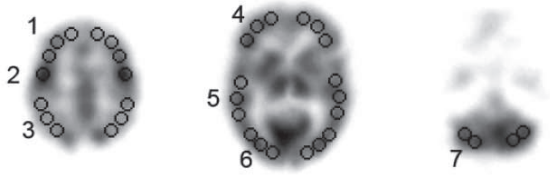

Fig. 1 ROIs on 3 transaxial slices.

3D-SSP

3D-SSP created with the Neurological Statistical Image Analysis Software (NEUROSTAT) developed by Minoshima et al.[10,11] was used to evaluate the spatial distribution of abnormal CBF. NEUROSTAT anatomically normalizes the individual SPECT data to the standard brain. The rCBF images were reconstructed in parallel with the anterior commissure—posterior commissure (AC-PC) line with a width of 2.25 mm. Three transaxial images were used: an image 17 slices above AC-PC line, and an image 2 slices above and 17 slices below it. Paired right and left circular (7 pixels diameter) regions of interest (ROI) were automatically drawn on the cortex (superior and inferior frontal cortex, motor cortex, parietal cortex, anterior and posterior temporal cortex, and medial temporal cortex) in the cerebral hemispheres and cerebellar hemispheres (Fig. 1). The relative CBF was calculated by dividing the blood flow in the cerebral cortex by the blood flow in the cerebellum. The mean CBF (mCBF) was the mean of all cortical ROIs.

NEUROSTAT extracts maximum cortical activity to adjacent predefined surface pixels on a pixel-by-pixel basis using a 3D-SSP technique.[10] Normalized activity of each patient was compared with the normal database. The

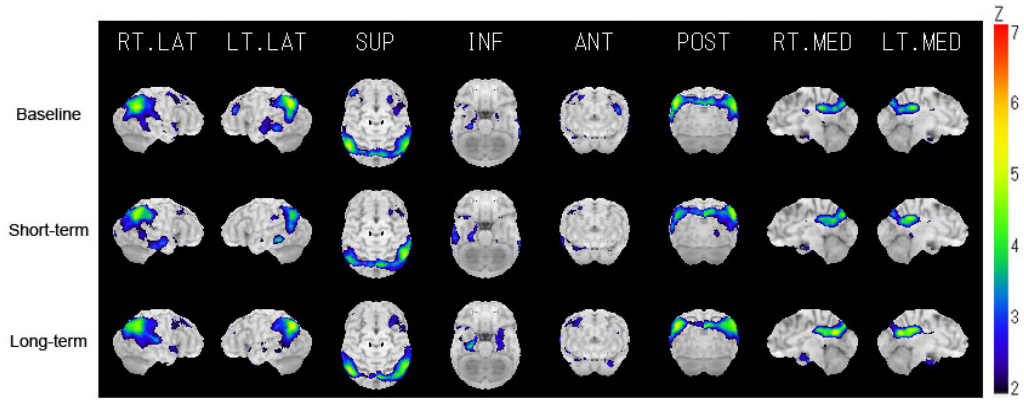

Fig. 2 Statistical maps showing decrease of rCBF adjusted to wholebrain counting in patients with AD at baseline, short-term and long-term compared to normal subjects.

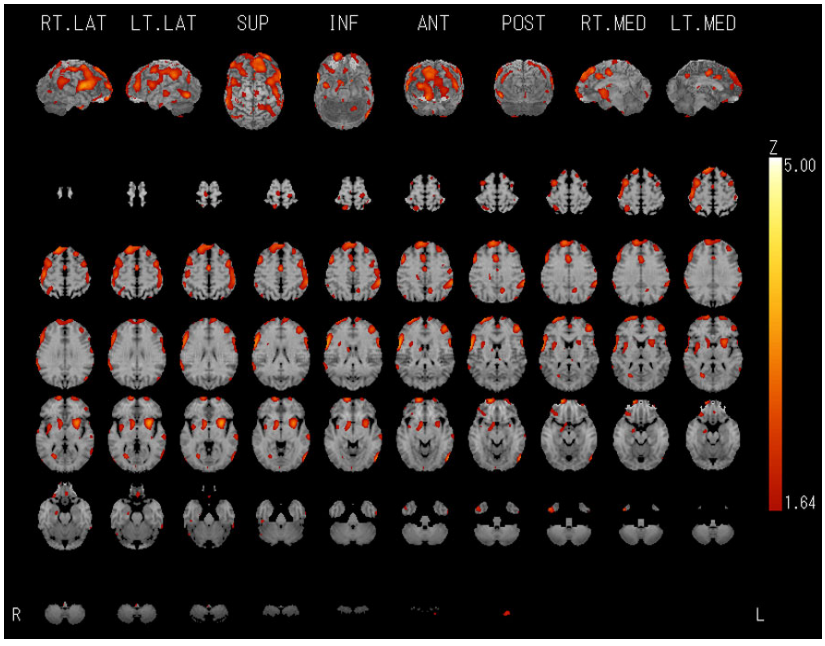

Fig. 3 3D-SSP Z score maps of increased CBF in short-term therapy compared with pre-treatment. Significant rCBF increase spread in each cortex: right lateral (RT. LAT), left lateral (LT. LAT), superior (SUP), inferior (INF), anterior (ANT), posterior (POST), right medial (RT. MED) and left medial (LT. MED) views are shown.

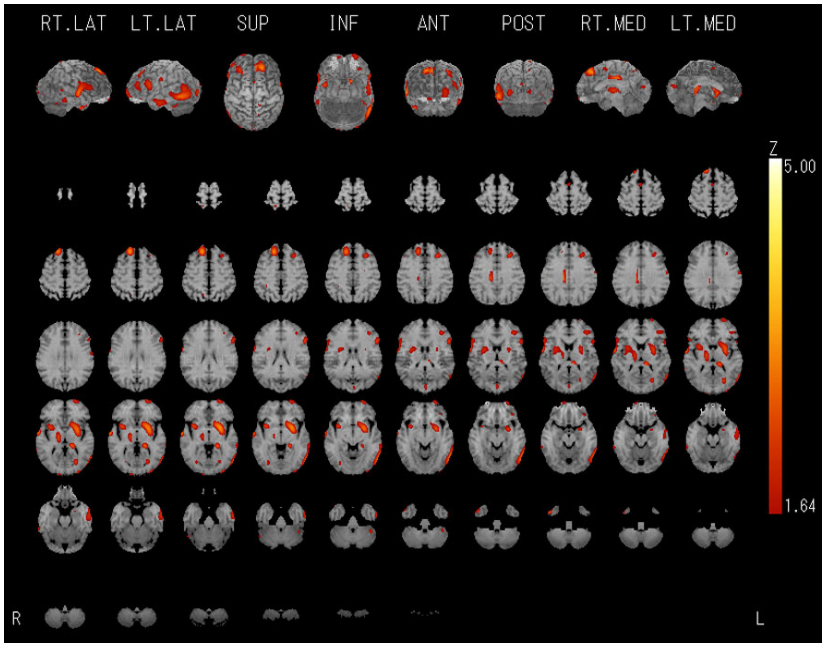

Fig. 4 3D-SSP Z score maps of increased CBF in long-term therapy compared with pre-treatment. The range of a significant increase decreased obviously compared to short-term therapy: right lateral (RT. LAT), left lateral (LT. LAT), superior (SUP), inferior (INF), anterior (ANT), posterior (POST), right medial (RT. MED) and left medial (LT. MED) views are shown.

normal database is composed of two categories depending on age: 9 subjects between 45 and 65 y, and 15 subjects between 66 and 84 y. We used the computer software iSSP3.5_2tZ in the iSSP (Version 3.5, Nihon Medi-Physics Co., Ltd.) for comparison between AD patients and normal subjects.

To demonstrate regional patterns of CBF changes after therapy, one-sample t-test values were calculated on a pixel-by-pixel basis between the baseline and short-term and between the baseline and long-term. Whole brain counting performed normalization. For these comparisons, we used a threshold Z score > 1.64, which corresponded to a p value < 0.05 (one sided). In the case of the use of two-sided test, the cutoff Z score is 1.96. In this study, a correction for multiple comparisons was not used.

Statistical Analysis

Statistical analysis was performed with Stat View software for Windows (HULINKS Co., Ltd.). The paired t test was used to compare differences between means in patients before and after treatment and differences between baseline, short-term, and long-term were tested with the Friedman repeated measures analysis of variance on ranks. P value < 0.05 was considered statistically significant.

RESULTS

Regional CBF in the AD group before and after therapy were compared with that of the normal control group. A reduction of rCBF was observed in the bilateral parietal and temporal cortices, the posterior cingulate gyrus and precuneus. After 3 months, the areas with rCBF reduction became narrower. At endpoint, lateral sides showed a similar reduction pattern and rCBF in the bilateral inferior temporal cortices, the posterior cingulate gyrus and precuneus decreased compared to baseline (Fig. 2).

The MMSE score was 21.2 ± 4.9 at baseline, 22.5 ± 3.5 after 3 months, and 20.7 ± 4.0 after one year. Neurologists assessed the response to donepezil treatment by MMSE score, clinical judgment and evaluation of caregivers after 3 months. The subjects were divided into 11 responders and 6 non-responders. No significant differences in rCBF between the responders and non-responders were found at baseline, short-term or long-term.

Table 1 shows a comparison of absolute CBF and relative CBF values of all patients for the short-term and long-term therapy. Post-treatment absolute CBF at the end of short-term therapy showed changes similar to those before therapy, and the CBF slightly decreased following the long-term therapy. On the other hand, significant increases in relative CBF were noted in the left frontal and parietal cortex, and right superior frontal cortex. The baseline and follow-up relative mCBF values were 0.765 ± 0.059 and 0.812 ± 0.115, respectively. The CBF was decreased after the long-term medication, whereas the CBF was still increased to a slight extent, as compared with the pre-treatment levels. Mean CBF significantly changed among the three groups.

Figure 3 shows three-dimensional views of increased CBF in short-term therapy compared with baseline. Statistical maps demonstrated that rCBF increase spread in each cortex. No significant rCBF reduction in the cerebral cortices was observed. Figure 4 shows increased CBF in long-term therapy compared with baseline. Regions of rCBF increase were still found in the frontal lobe and in the left temporal lobe, but the range of a significant increase decreased obviously compared to short-term therapy. CBF was slightly decreased in the posterior cingulated gyrus.

DISCUSSION

Cholinergic neurons project to the cerebral cortex and amygdala, and their highest density is in the limbic system, including the hippocampus and amygdaloid nuclei, and in the association area of the cerebral cortex. Reduced cholinergic neuron activity caused by degeneration of Meynert's nucleus has been shown to be related to the memory impairment in AD.[12] The symptoms of AD patients can be divided into core symptoms attributable to the brain damage and peripheral symptoms that develop secondarily. The former include memory disorders, disorientation, and impaired judgment, and drugs that have efficacy against core symptoms are referred to as anti-dementia drugs. The development of AChE inhibitors as anti-dementia drugs for AD has progressed, and donepezil has been developed as a new AChE inhibitor for clinical use following tacrine.[13]

Studies in the United States, Europe and Japan have shown significant increases in scores on the Alzheimer's Disease Assessment Scale (ADAS) from 12 to 24 weeks in donepezil groups compared to placebo groups.[3,14,15] In a study on long-term administration Rogers et al. reported that evaluation of cognitive function by ADAS-cog scores showed that it was possible to maintain the baseline scores until 38 weeks after the start of administration, and although the scores began to decrease thereafter, the tendency to decrease was milder than in the natural course of AD in untreated patients.[16] After short-term administration, the relative mCBF and rCBF in the some cortices increased, but after one year or more, the CBF had decreased to below the blood flow value at 3 months and was still slightly higher than before administration. This was the same as the changes in cognitive function after donepezil administration and showed that it is possible to evaluate the efficacy of donepezil by blood flow measurements as well. AChE inhibitors increase neuronal activity by inhibiting the reuptake of ACh secreted by nerve endings and increasing its concentration, and activation of the remaining neurons improves the symptoms. However, absolute CBF did not vary significantly among the three groups. Absolute cerebellar blood flow was slightly

decreased as of 3 months after the start of donepezil administration, while cerebral blood flow was unchanged. Statistical analyze by 3D-SSP adjusted to whole brain counting showed a relative rCBF increase in cerebral cortex. The range of physiological fluctuations must be taken into account in absolute CBF, so these findings raise the possibility that the donepezil yields a mild increase in CBF of the cerebral cortex and dose not affect CBF in the cerebellum. After one year the absolute CBF values in the all cortices showed slightly lower values than at baseline. It is inferred by analogy from the pharmacodynamics of donepezil that it is incapable of arresting the neuronal degeneration itself, and these results are a reflection of the fact that the nerve degeneration had progressed.

The many authors that evaluate rCBF changes in patients undergoing donepezil therapy use relative CBF.[4, 17,18] Our results showed no significant differences in rCBF between responders and non-responders, but were also similar to current reports. CBF is coupled to neuronal activity. Therefore it is possible to indirectly evaluate the pharmacological efficacy of anti-dementia drugs by measuring CBF by SPECT. The change in absolute CBF was approximately 10% of the value before treatment and was within the range of physiological fluctuations, and so the relative value should be used for evaluations of CBF changes after drug therapy.

CONCLUSION

A significant increase in relative rCBF was evident in the short-term donepezil therapy group, while following the long-term therapy, rCBF decreased to the pre-treatment level. Absolute rCBF showed minimal change and a tendency to decline regardless of treatment with donepezil.

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