AUDITORY P300 EVENT-RELATED POTENTIALS AND MINI MENTAL STATE EXAMINATION PERFORMANCE IN DEMENTIA ; EFFECTS OF IDEBENONE AND VINPOCETINE

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Abstract: One group of twenty-one demented patients were administered Idebenone 90 mg/day for eight weeks, the other group of thirty-two demented patients were administered Idebenone 90 mg/day plus Vinpocetine 15 mg/day for eight weeks. Mini Mental State Examination (MMSE) was carried out and auditory event-related potentials (ERPs) were recorded pre-treatment, after four weeks treatment and after eight weeks treatmet. MMSE performance was significantly improved with treatment in both groups. Central P300 latency was shortened in the group which was treated with Idebenone and Vinpocetine, but not in the group which was treated with Idebenone alone. Based on the obtained results, we were convinced that administration of Idebenone and Vinpocetine was very useful in the treatment of vascular dementia.

Index Terms

vascular dementia, event-related potentials (ERPs), Idebenone, Vinpocetine

INTRODUCTION

Event-related potentials (ERPs), recorded using relatively simple, noninvasive techniques, offer a versatile approach to investigating cognitive changes and brain structural abnormalities in psychiatric disorders. Many studies have examined the P300 response in normal aging and dementing illnesses, in particular Alzheimer's disease and vascular dementias, and those dementias associated with Huntington's disease, Parkinson's disease, human immunovirus (HIV) infection, and Down's syndrome. Yet, as discussed by Goodin[1] and Pfefferbaum et al[2], the rather low sensitivity and specificity of P300 changes in dementia may restrict its clinical usefulness as an aid to diagnosis or as a tool for measuring specific cognitive impaiments in these conditions. However, the utility of such as the P300 depend on the exact clinical question being asked rather than on "an arbitrary definition of what constitutes acceptable levels of sensitivity or specificity." The delay of P300 latency reflects the degree of cognitive delcine in demented patients[3]. The P300 response might be expected to be useful for evaluating the pharmacotherapy in dementing illness. To examine the effects of Idebeone and Vinpocetine, we

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treated demented patients with these nootropic drugs, and investigated their P300 latency and Mini Mental State Examination (MMSE) performance before and after the treatment.

SUBJECTS AND METHODS

The subjects were fifty-three outpatients of Nara Medical University Hospital. All agreed to participate in the study and were able to give informed consent. According to ICD-10, thirty-nine subjects met the criteria for vascular dementia, eleven subjects met the criteria for dementia in Alzheimer's disease, two subjects met the criteria for somatoform disorders and one snbject met the criteria for dementia in other specified diseases classified elsewhere (brain tumor). The subjects were divided into two groups, one group treated with Idebenone (Idebenone group) and the other group treated with Idebenone and Vinpocetine (Idebenone & Vipocetine group). Table 1 and Table 2, and Table 3 show the demographic characteristics of the groups. There was no significant difference between the two groups.

All participants included in the study were physically healthy and had no history of substance abuse. Specifically excluded from the study were those with the following conditions : 1) severe dementia, making patients unable to generate a recognizable or reproducible response ; 2) pseudodementia due to depression ; 3) disturbance of consiousness ; 4) concurrently receiving augmentation of antidepressants, neuroleptics, anticholinergics, or any other medications with potentially effects on P300 latency and MMSE performance.

The subjedts of the Idebenone group were treated with Idebenone 90 mg/day for 8 weeks, while the subjects of the Idebenone & Vinpocetine group were treated with Idebenone 90 mg/day plus Vinpocetine 15 mg/day for 8 weeks. The MMSE performance of the subjects was evaluated at three time points : 1) before treatment ; 2) after 4 weeks of treatment ; 3) after 8 weeks of treatment. P300 latency was studied at the same three time points.

Table 1. Demographic characteristics of subjects

	Idebenone group (N=21)		Idebenone Vinpocetine group (N=32)	
	N	(%)	N	(%)
Male	8	(38.1)	11	(34.4)
Female	13	(61.9)	21	(65.6)
Diagnosis				
Vascular dementia	15	(71.4)	24	(75.0)
Alzheimer's disease	4	(19.0)	7	(21.9)
Others	2	(9.5)	1	(3.1)
Age (ys)	Mean	(SD)	Mean	(SD)
Total	67.7	(17.6)	67.0	(15.2)
Male	66.3	(10.5)	65.0	(10.3)
Female	68.5	(10.7)	68.1	(17.1)
Vascular dementia	66.9	(19.8)	67.2	(16.8)
Alzheimer's disease	75.0	(5.8)	70.4	(6.3)
Others	59.0	(6.0)	56.0	(0)

Table 2. Characteristics of two diagnostic groups before treatment

	Vascular dementia group (N=39)		Alzheimer's type dementia group (N=11)	
	Mean	SD	Mean	SD
Age (year)	67.05	18.29	72.09	6.82
MMSE scores treatment	22.65	5.36	18.64	5.67*
Central P300 latency before treatment (msec.)	366.7	47.2	384.3	33.1
Parietal P300 latency before treatment (msce.)	370.3	51.9	390.3	45.1
Central P300 amplitude before treatment (μV)	5.87	3.12	4.54	3.07
Parietal P300 amplitude before treatment (μV)	6.76	3.13	5.00	3.13

*$P<0.05$ paired t-test

Table 3. Characteristics of two groups before treatment

	Idebenone group (N=21)		Idebenone Vinpocetine group (N=32)	
	Mean	SD	Mean	SD
MMSE scores before treatment	22.43	5.43	21.59	5.81
Central P300 latency before treatment (msec.)	356.0	39.5	376.6	45.0
Parietal P300 latency before treatment (msec.)	363.4	50.2	377.2	50.0
Central P300 amplitude before treatment (μV)	6.03	3.23	5.49	3.02
Parietal P300 amplitude before treatment (μV)	6.94	3.30	6.07	3.02

no statistically significant difference was observed between groups

All ERPs recordings were made in a sound-attenuated room, with each subjects seated in a comfortable armchair. Unipolar recordings referred to the ear lobes were made between silver /silver chloride electrodes at central (CZ) position and parietal (PZ) position according to the 10-20 electrode system. For the oddball paradigm, ERPs were elicited with binaural 1000 (standard) and 2000 (target) Hz tones. The stimulus probability was set at 2/8 (target : standard), the stimuli were generated in a random series once every 2.0 sec. Tones of 100 msec duration were generated at 1000 Hz and 2000 Hz and were delivered binaurally at 80 dB SPL through headphones. The subjects were informed that they would hear low-pitched (1000 Hz) tones interspersed occasionally with high-pitched (2000 Hz) tones, and that they were required to press the button at the high pitched tones. Recordings were considered satisfactory if counting error was less than 10 %. Subjects were instructed to relax and to keep as still as possible during the test. Data were obtained with a sampling rate 500 Hz (analog lowpass filter of 150 Hz) from 110 msec prestimulus to 1000 msec poststimulus. Thirty-two sweeps were recorded for the high-pitched tone. For artifact suppression, all trials were automatically excluded from averaging when the voltage exceeded 50 μV absolute size at any point during the averaging period. The sweeps were then averaged for each subject. P300 amplitude was measured as the difference in voltage between the baseline and the higher point between 250 and 550 msec after the stimulus. The P300 latency (msec) was measured by the least-mean-square method[4].

RESULTS

Effect of medication on MMSE performance

Table 4 shows the effect of the treatment on MMSE performance. In the total group, the MMSE performance was significantly improved after 4 weeks and after 8 weeks of treatment. These treatments were effective for vascular dementia, but not for dementia in Alzheimer's

Table 4. Effect of medication on MMSE performance

	N	MMSE score		
		Before treatment	After 4 weeks of treatment	After 8 weeks of treatment
Total	53	21.93±5.62	23.19±5.47**	24.45±5.38***
Diagnosis				
VD	39	22.66±5.37	24.45±4.65**	25.84±4.08***
ATD	11	18.64±5.68	17.55±4.61 n. s.	19.00±6.00
Others	3	26.67±2.52	29.33±1.15 n. s.	29.33±0.89
Treatment				
1 Group	21	22.43±5.43	23.52±5.56*	24.52±5.86**
MMSE>20	14	25.64±2.59	26.79±3.07*	27.64±3.73*
MMSE≦20	7	16.00±3.37	17.00±2.83 n. s.	18.29±4.03*
2 Group	32	21.59±5.81	22.97±5.49*	24.40±5.14***
MMSE	19	25.47±2.93	26.63±4.60*	27.32±3.28*
MMSE≦20	13	15.92±3.95	19.08±4.29*	20.15±4.38***

VD=Vascular dementia
AD=Dementia in Alzheimer's disease
1 group=patients treated with Idebenone
2 group=patients treated with Idebenone and Vinpocetine
*P<0.05 **P<0.01 ***P<0.001 paired t-test
compared with before treatment

Table 5. Effect of medication on ERP (P300) latency

	N	Central P300 latency (msec.)		
		Before treatment	After 4 weeks of treatment	After 8 weeks of treatment
Total	53	372.48±43.54	369.42±42.98	360.44±46.17
1 group	21	360.82±39.48	359.29±36.20	363.58±32.08
2 group	32	378.87±44.93	374.97±45.88	358.38±53.91*
	N	Parietal P300 latency (msec.)		
		Before treatment	After 4 weeks of treatment	After 8 weeks of treatment
Total	53	373,73±48.45	368,17±47.52	362.52±47.19
1 group	21	364.29±45.68	353.82±38.54	362.58±34.38
2 group	32	378.90±49.87	376.03±50.64	362.48±54.58

1 group=patients treated with Idebenone
2 group=patients treated with Idebenone and Vinpocetine
*P<0.05 paired t-test

disease. In both the Idebenone group and the Idebenone & Vinpocetine group, the MMSE performance was significantly improved after 4 weeks and after 8 weeks of treatment. Each group was divided into two subgroups, one scoring more than 20 (subgroup 1), and one scoring less than 21 (subgroup 2). In the Idebenone group, the subgroup 1 showed significant improvement after 4 weeks and after 8 weeks of the treatment, while the subgroup 2 showed significant improvement only after 8 weeks of the treatment. In the Idebenone & Vinpocetine group, both

subgroups showed significant improvement after 4 weeks and after 8 weeks of the treatment. For the mildly and moderately demented patients (those scoring less than 21 on the MMSE), the administation of Idebenone & Vinpocetine was more effective at MMSE performance than the administration of Idebenone alone ($P<0.05$, chi-square test).

Effect of medication on ERPs

The mean and SD of the latencies and amplitudes for central and parietal P300 are shown in Table 5, Table 6, Table 7 and Table 8. The amplitudes for central and parietal P300 remained unaffected by treatment. The latency for parietal P300 remained unaffected by treatment whereas the latency of central P300 was significantly ($P<0.05$) decreased from

Table 6. Effect of medication on ERP (P300) amplitude

	N	Central P300 amplitude (μV)		
		Before treatment	After 4 weeks of treatment	After 8 weeks of treatment
Total	53	5.70±3.09	5.28±4.26	5.70±3.08
1 group	21	6.03±3.23	4.46±4.19	3.87±2.93
2 group	32	5.49±3.02	5.82±4.28	6.57±5.21
	N	Parietal P300 amplitude (μV)		
		Before treatment	After 4 weeks of treatment	After 8 weeks of treatment
Total	53	6.42±3.13	5.89±3.34	5.76±3.77
1 group	21	6.94±3.31	5.39±3.69	5.78±3.65
2 group	32	6.07±3.02	6.23±3.11	5.75±3.91

1 group=patients treated with Idebenone
2 group=patients treated with Idebenone and Vinpocetine
No statistically significant difference was observed
compared with before treatment : paired t-test

Table 7. Effect of medication on ERP (P300) latency in two diagnostic groups

	N	Central P300 latency (msec.)		
		Before treatment	After 4 weeks of treatment	After 8 weeks of treatment
VD	39	365.23±44.13	368.29±50.11	354.77±45.76
ATD	11	385.40±34.74	371.90±27.46	378,00±50.54
	N	Parietal P300 latency (msec.)		
		Before treatment	After 4 weeks of treatment	After 8 weeks of treatment
VD	39	372.97±49.22	369.26±48.12	358.52±45.68
ATD	11	392.00±47.12	369.00±51.75	379.70±54.76

VD ;=Vascular dementia
AD ;=Dementia in Alzheimer's diseas
no statistically significant difference was observed
compared with before treatment : paired t-test

Table 8. Effect of medication on ERP (P300) amplitude in two diagnostic groups

	N	Central P300 amplitude (μV)		
		Before treatment	After 4 weeks of treatment	After 8 weeks of treatment
Total	53	5.70±3.09	5.28±4.26	5.70±3.08
1 group	21	6.03±3.23	4.46±4.19	3.87±2.93
2 group	32	5.49±3.02	5.82±4.28	6.57±5.21
	N	Parietal P300 amplitude (μV)		
		Before treatment	After 4 weeks of treatment	After 8 weeks of treatment
Total	53	6.42±3.13	5.89±3.34	5.76±3.77
1 group	21	6.94±3.31	5.39±3.69	5.78±3.65
2 group	32	6.07±3.02	6.23±3.11	5.75±3.91

1 group=patients treated with Idebenone
2 group=patients treated with Idebenone and Vinpocetine
no statistically significant difference was observed between groups: t-test

378,87 msec to 358.38 msec in the Idebenone & Vinpocetine group after 8 weeks of treatment. The vascular dementia and dementia in Alzheimer's disease groups did not differ significantly at the amplitudes and latencies. MMSE score before treatment was not a significant factor of the effect on ERPs (data not shown). An ANOVA was carried out with central P300 latency at each item of MMSE as covariate. Any item of MMSE was not a significant covariate with central P300 latency. There was no gingificant correlation between the change of MMSE score and the change of the latencies for either central or parietal P300.

DISCUSSION

The Mini Mental State Examination, which includes brief tests of language functioning and praxis, has been shown to be useful in gaining information from neurological patients in areas or memomy and other congitive functions. A composite score may be obtained and those who score 23 or less out of 30 are considered to be intellectually impaired. It is notable that community stuby only approximately one third of people scoring below this threshold were diagnosed as having dementia, the rest having neither disorder nor other psychiatric problems. No-one scoring above 23 was subsequently diagnosed as having dementia. Performance on the MMSE tends to be highly correlated with variation of the Dementia Rating Scale[5,6].

The cerebral potentials associated with infomation processing, especially the timing of sensory stimulus discrimination and categorization together with the reaction time measures, provide a unique means of separating decision processes from motor involvement. These ERPs are insensitive to physical characteristics of the stimulus but are primarily affected the task associated with simulus discrimanation which requires the subject to distinguish a particular target stimulus from a randomly presented sequence of two or more different types of stimuli. This paradigm yields an ERPs complex comprising components N1, N2, and P3 (P300). N1, a negative potential occurring around 100 msec after stimulus onset is considered to represent the encoding of auditory stimulus[7]. N2 is a second negative peak occurring around 200 msec

after stimulus which may represent the input stage of the stimulus evaluation process[8]. P3, or P300, a positive potential with respect to the pre-stimulus baseline with a modal latency of 300 msec reflects motor-free speed of cognitive processing. A P300 is prolonged in latency and reduced in amplitude with advancing age and with the difficulty of target identification[9]. In 1978 Goodin et al.[10] reported that, in a group of patients with dementia of varying etiologies, 80 % had abnormally long P300 latencies relative to age norms. Subsequent investigation from this groups[11] revealed normalization of P300 latency in some neurological patients whose dementia reversed with treatment.

Vinpocetine, a synthetic ethyl ester of apovincamine, is reported to increase cerebral blood flow meaured by regional cerebral blood flow techniques by reducing blood viscosity and platelet aggregation[12]. Double-blind studies comparing Vinpocetine with a placebo in patients with vascular derentia or Alzheimer's disease showed significant reduction in all scales of the Sandoz Clinical Assessment Geriatric Scale within 60-90 days[13,14]. Idebenone is a benzquinone, synthetic Ubiquinone homolog, functioning as an electron carrier in the mitochondrial respiratory chain through the cytochrome *b* chain and as an antioxidant against membrane damage caused by lipid peroxidation in brain mitochondria[15]. It has been shown that Idebenone is useful in the treatment of patient of ptients with cerebrovascular disorders and particularly effective for subjective and psychotic symptoms[16].

This study showed that treatment both with Idebenone and with Idebenone & Vinpocetine improve MMSE performance of the patients and that this improvement was observed only in the vascular dementia patients. Therefore these drugs were effective for vascular dementia, but not effective for dementia in Alzhedimer's disease. Amyloid protein might play a major role in the process of Alzheimer's disease[17]. It is necessary to develop new drugs involving this process for treatment of dementia in Alzheimer's disease.

Administration of Idebenone alone improved MMSE performance, but had no effect on P300 latency, which contradicts some reports[18] Idebenone shortened the latencies of 300 in patients with dementia after 8 weeks. This discrepancy between the results suggests that ERPs may be much more stable and less sensitile to mild psychotropics such as nootropic agents. It might be the reason why tasks based on oddball paradigm were too simple for cognitive evaluation. The oddball talk itself appears to have some senstivity to dementia. Indeed, the prologation of P300 latency in dementia may tell us something of the pathophysiology of the disorder. The oddball task is but one of a number of paradigms that could be used to elicit a P300, and some investigators have suggested the use of more specific tasks to examine more specific cognitive dysfunctions. A paradigm that would reliably elicit a P300 without requiring an overt response or the performance of a task would have additional potential value for patients who could not or would not respond or perform the task.

This stuby also showed that combined administration of Idebenone and Vinpocetine was more potent for improvement for MMSE performance of the mildly and moderately demented patients than administration of Idebenone alone and that the effect of combined administration of them for cognitive processing was more sufficient to reduce central P300 latency than administration of Idebenone alone. It is believed in clinical practice that combined therapy of one drug of blood viscosity reducers or vasodilators and one of metabolic enhancers is very useful in the treatment of dementia in cerebrovascular disease. Our results support this therapy

theoretically.

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