

## Clinical Research

# The Effects of Rivastigmine in Parkinson's Disease Dementia: An Electrophysiological Study

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### ABSTRACT

**Objective:** Rivastigmin has been shown to improve cognition in patients with Parkinson's disease dementia (PDD) without any remarkable negative effects on the motor function of the patients. In this study, we evaluated positive effects of rivastigmine therapy on cognition in PDD by means of behavioral inventory and neuropsychological tests and P300. In addition, we investigated the patients clinically and electrophysiologically using movement related cortical potentials (MRCP) and reaction time (RT) to show whether there are any negative effects of rivastigmin on motor function.

**Material and Method:** Ten idiopathic Parkinson's disease (PD) patients and 9 PDD patients were included to the study. Patients were assessed by neuropsychological test battery and also neurophysiological tests (P300, MRCP and RT) before rivastigmine treatment and after the sixth month of treatment.

**Results:** PDD patients showed statistically significant improvement in neuropsychological tests related memory and shortening of P300 latency. However, we didn't find any statistically significant changes in the measurements of MRCP and RT tests after therapy.

**Conclusion:** Our study has suggested that while rivastigmine therapy improve cognitive functions in PDD, it doesn't cause any side effects on motor function of patients.

**Keywords:** Parkinson's Disease Dementia, P300, Rivastigmine.

### ÖZET

#### Parkinson Hastalığı Demansında Rivastigminin Etkisi: Elektrofizyolojik Bir Çalışma

**Amaç:** Rivastigminin Parkinson hastalığı demansı (PDD) olan hastalarda motor fonksiyonlar üzerinde herhangi kayda değer olumsuz bir etkisi olmaksızın bilişiyonu iyileştirdiği gösterilmiştir. Bu çalışmada, Parkinson demansında rivastigmin tedavisinin bilişiyon üzerindeki olumlu etkisi klinik olarak bilişiyonu değerlendiren nöropsikolojik testler, davranışsal envanter ve nörofizyolojik olarak da P300 ile değerlendirilmesi planlanmıştır. Ayrıca klinik olarak Birleşik Parkinson Hastalığı Derecelendirme Ölçeği (UPDRS) ile ve elektrofizyolojik olarak da harekete ilişkin kortikal potansiyeller (HİKP) ve reaksiyon zamanı (RZ) ile de tedavi süresince ilacın motor fonksiyonlara herhangi bir olumsuz etkisinin olup olmadığı incelenmiştir.

**Gereç ve Yöntem:** Dokuz Parkinson demansı hastası ve 10 idiopatik Parkinson hastası çalışmaya dahil edilmiştir. Demansı olan Parkinson hastalarına rivastigmin tedavisi öncesinde ve tedavinin 6. ayında bellek, yürütücü fonksiyonlar, dikkati değerlendiren nöropsikolojik test bataryası ve nörofizyolojik testler (P300, HİKP ve RZ) uygulanmıştır.

**Bulgular:** Altıncı ayın sonunda Parkinson demansı hastalarında bellek ile ilgili nöropsikolojik testlerde anlamlı bir düzelme saptanmıştır. Nörofizyolojik testlerden bilişiyon ve dikkati değerlendirdiğimiz P300'de de tedavi sonrasında latans kısalması görülmüştür. Bu bulgularla beraber rivastigminin olası motor yan etkileri açısından değerlendirdiğimiz HİKP ölçümlerinde ise kötüleşme saptanmamıştır.

**Sonuç:** Rivastigmin Parkinson demansında kognitif fonksiyonları düzeltirken motor fonksiyonlar üzerinde olumsuz bir yan etki oluşturmamıştır.

**Anahtar Sözcükler:** Parkinson Hastalığı Demansı, P300, Rivastigmin.

Dementia is a non-motor symptom frequently encountered in patients with Parkinson's disease (PD); the prevalence averages 40% and the annual incidence, ~10% (1, 2). In patients with Parkinson's disease dementia (PDD), the progress of particular types of dementia may be evaluated using data from clinical and neuropsychological tests. It is also possible to monitor the development and, to some extent, the severity, of dementia, using the P300 test, which is an electrophysiological technique (3). The latter test yields infor-

mation on brain pathways associated with attention and memory; the P300 amplitude decreases and the peak latency increases as the severity of cognitive dysfunction advances (4, 5). The P300 test is also used to evaluate the effectiveness of treatment in Alzheimer's disease (AD) patients, because cognitive functional disorders are correlated with changes in P300 data. The P300 latency decreased in line with recovery of cognitive functioning at week 24 after initiation of a particular treatment in AD patients (6). Although no effective

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treatment for PDD has been available until recently, cholinesterase inhibitors used to treat AD have been found to be useful in this context. A double-blind, placebo-controlled study found that, at the end of 24 weeks, the acetylcholinesterase inhibitor rivastigmine significantly improved (compared to placebo) general performance, cognition, attention, executive functioning, the ability to engage in daily activities, and the neuropsychiatric symptoms, of PDD patients (7). It was noted that, as in AD patients, rivastigmine was well-tolerated and did not cause serious side-effects, but could aggravate PD-associated tremor in the long term (8). In the current study, we explored the influence of rivastigmine on cognition, evaluated both clinically (using cognition-related neuropsychological tests and behavioral inventories) and neurophysiologically (employing the P300 test). We measured movement-related cortical potential and reaction time to determine whether the drug influenced motor function.

## MATERIAL and METHOD

Two groups of patients treated in the Neurology Polyclinic of Akdeniz University were included in the present study. One group was diagnosed with idiopathic PD without dementia and the other with PD and dementia. The Ethics Committee of Akdeniz University approved the study and all patients signed informed consent forms. Test group (PD patients with dementia): These patients were diagnosed with PDD using the DSM-IV criteria. The diagnosis was made on the basis of results of the tests listed below, in line with literature indications (9). Drug regimes were not changed during the study, and dose changes were made only in extraordinary circumstances.

- 1- A diagnosis of PD,
- 2- PD diagnosis must have preceded diagnosis of dementia by at least 2 years,
- 3- MMSE score <26,
- 4- The activities of daily life were compromised by dementia,
- 5- At least two of the cognitive functions listed below must have been compromised:
  - a) Naming months backwards or counting backwards from 100 in increments of 7 (at least two mistakes),
  - b) Verbal fluency or ability to draw a clock,
  - c) MMSE pentagon drawing,
  - d) Recalling three words.
- 6- Absence of major depression, as shown using the Geriatric Depression Scale [GDS],
- 7- Absence of delirium,
- 8- Absence of any disease with an uncertain diagnosis.

Control group (PD with no dementia): This group contained idiopathic PD patients. PD was diagnosed by clinical examination (resting tremor, cogwheel rigidity, bradykinesia/akinesia, postural instability, and flexor posture) using the UK PD society Brain Bank clinical diagnostic criteria. Dementia was excluded using the tests described above. We excluded patients diagnosed

with secondary parkinsonism (caused by infection, drugs, toxins, vascular disease, trauma, or an intracranial mass), Parkinson-plus syndromes, any inherited degenerative disease, major depression, or delirium; These latter conditions were excluded by history-taking, clinical examination, and brain magnetic-resonance imaging and any patient for whom rivastigmine was contraindicated. Patients who met the inclusion criteria completed forms giving demographic details. We recorded the findings of clinical examinations, and drugs used. In addition, the "Unified Parkinson's disease Rating Scale" (the UPDRS) and the Hoehn and Yahr Staging (HYS) module were administered to all patients of both groups at months 0 and 6. To evaluate cognitive functioning, a neuropsychiatric test battery was administered to all patients, and P300 recordings were obtained. As acetylcholinesterase inhibitors used to treat PDD can exacerbate PD symptoms, Movement-Related Cortical Potential (MRCP) and Reaction Time (RT) tests were performed to evaluate such effects. In the test group, rivastigmine was slowly titrated upward after initial testing. The initial dose was 1.5 mg twice daily and was increased by 3 mg monthly. The maximum active best-tolerated dose was maintained. The average dose was 7.8 mg/day (range, 6-12 mg/day). Some patients who could not tolerate the side-effects of the drug were provided with drug-containing transdermal patches. All neuropsychological and neurophysiological tests were performed with patients in "drug-on" periods.

Neuropsychological testing was performed using a test battery administered over ~40–50 min that yielded information on various cognitive fields. Testing was conducted in a silent room and patients were not distracted. Daily life activities were evaluated using the Mini-Mental test (the MMSE) and the Instrumental Activities of Daily Living (IADL) Scale; the tests evaluated various cognitive fields. Patients deteriorated clinically as IADL scores increased. Accompanying psychiatric symptoms were evaluated using the neuropsychiatric inventory (NPI). All patients were administered the Rey Auditory Verbal Learning Test (Rey AVLT) to test verbal memory, the Wechsler Memory Scale Edition III (WMS-III) visual memory subtest to evaluate visual memory, and the trail-making test (parts A and B) and Luria's drawing test to assess executive functioning. The 'forward and backward digit span' test was used to evaluate attention; the Similarities Test to evaluate abstract reasoning; and the F-A-S Test to explore verbal fluency.

P300 recordings were obtained using the Nihon Kohden Neuropack 8 device. The electrode placement points were first specified, and the head cleaned using alcohol followed by rubbing with a gel that abraded the skin. Ag/AgCl disk electrodes were used during recording; active electrodes were placed on the Fz and Cz locations and the reference electrode on the earlobe. All patients wore headphones. The stimulation method was the standard auditory "oddball paradigm", which

required patients to distinguish and count treble tones (2 kHz) that were presented at a frequency of 20% of bass tones (1 kHz). Patients were asked to count the numbers of sounds with a treble tone. Each screen, analyzed at 1-s intervals, consisted of 10 small squares presented 0.1 s apart. Thirty potentials developing when targets (stimulants) were distinguished and counted were averaged, and the traces evaluated. The P300 latency and the peak-to-peak P300 amplitude were measured in each trace obtained from the Fz, Cz, and Pz electrodes.

Movement-Related Cortical Potential test recordings were obtained using the Nihon Kohden Neuropack 8 device. The electrode placement points were first specified, and the head cleaned using alcohol followed by rubbing with a gel that abraded the skin. Ag/AgCl disk electrodes were used during recording; active electrodes were placed at the C3, Cz, and C4 locations, and the reference electrode on the earlobe. To trigger the MRCP wave complex, patients were instructed to perform intermittent wrist extensions, and EMG activities were measured via surface electrodes placed on the musculus extensor digitorum communis. The frequency limits were maintained at 0.1-50 Hz. The total analysis time was 5 s, including "back averaging" commencing 3,500 ms before EMG activity. An average of 20 MRCP responses was collected. The test was performed twice and traces from the C3, Cz, and C4 electrodes were analyzed for: (a) Latency of the readiness potential, (b) amplitude of the readiness potential, (c) amplitude of the early readiness potential, (d) amplitude of the late readiness potential, (e) latency of skilled performance positivity, and (f) amplitude of skilled performance positivity. Two measurements were used to estimate the latency of the readiness potential; these were: (a) Time from when pre-motion negativity commenced to when EMG activity commenced, and (b) time from when pre-motion negativity commenced to when the negativity peaked.

To measure reaction time (RT), each patient, with both eyes open, was seated (twice) in front of a monitor, at a distance of at least 1 m. The monitor was used to record visually stimulated potentials. Black-and-white squares were used as stimuli. Induction of a stimulus ensured triggering of the device. Each stimulus was induced by the technician administering the test, without prior notice to the patient, and the patient was asked to make a quick extension of the wrist as soon as the color of the squares on the screen changed. Simultaneously, EMG activities were measured via surface electrodes placed on the musculus extensor digitorum communis. The analysis time was 1 s. The latency to the time of commencement of EMG activity was taken to be the reaction time latency.

The SPSS software was used to perform statistical analyses. Wilcoxon's rank-sum test was used to analyze descriptive data, and a paired samples t-test to compare data from the test and control groups obtained at months 0 and 6.

## RESULTS

Fourteen PD patients without dementia and nine PDD patients were included. One patient from the former group was excluded because they could not complete all tests, and a further three patients from the same group were excluded because they did not return for evaluation at month 6. Thus, the former group finally included 10 patients. PDD patients took an average daily dose of 506.9-mg levodopa; the average dose in the (PD) control group was 455.3 mg. Dopamine agonists were used principally by the control group; these were pramipexole, ropinirole and piribedil.

Initially, when data from the two groups were compared, no significant differences were found in the UPDRS and HYS scores ( $p=0.19$ ). When IADL scores were compared, the PDD (test) group scored significantly higher than the control group (13.3 vs. 5.9;  $p=0.01$ ). The total NPI score did not differ significantly between the two groups (6.7 vs. 2.7;  $p=0.39$ ). Also, no significant difference was identified in NPI sub-group analyses. Demographic data of all patients are shown in (Table 1).

**Table 1.** Socio-demographic and clinical aspects

	PD n=10	PDD n=9	p value
Age (years)	74,8 ± 6,1	64,3 ± 10,5	0,15
Gender	8/2	7/2	
Scholling level (years)	8,2 (3-15)	5,8 (4-11)	0,10
Duration of PD (month)	39 (12-72)	93,3 (48-204)	<b>0,01</b>
Duration of PDD (month)		18,6 (12-36)	
<b>UPDRS</b>	26,7 (16-46)	38,3 (21-69)	0,19
<b>HYS</b>	1,7 (1-3)	2,3 (2-3)	0,09
<b>NPI</b>	6,7 (0-30)	2,7 (0-9)	0,39
<b>IADL</b>	5,9 (5-8)	13,3 (7-26)	<b>0,01</b>

*PD: Parkinson disease, PDD: Parkinson Disease Dementia, UPDRS: Unified Parkinson's Disease Rating Scale, HYS: Hoehn an Jahr scale, NPI: Neuropsychiatric Inventory, IADL: Instrumental Activities of Daily Living*

After rivastigmine treatment, the MMSE score was significantly higher in the test (PDD) group at month 6 compared to the baseline value ( $p=0.04$ ), but this was not true of the control group. The AVLT-5 (assessing the influence of AVLT on learning) and AVLT-7 (measuring long-term memory) sub-parameters increased significantly in the test group by month 6 compared to the baseline values ( $p=0.04$ ,  $p=0.01$ , respectively). In the control group, the value of the AVLT-5 sub-parameter did not change over time, but a significant increase in the AVLT-7 value was evident at month 6 compared to baseline ( $p=0.007$ ). The K-A-S Test value increased significantly in the test group by month 6 ( $p=0.01$ ), but not in the control group. No significant 6-month change in WMS III Visual Memory sub-test data measuring early and late recall (subtests 1 and 2) was found in either group ( $p=0.1$  vs.  $p=0.3$ ; test vs. control). In terms of the WMS III similarity sub-test scores, a slight (but not significant) dif-

ference was evident between the two groups at month 6 ( $p=0.2$ ). The results of the trail-making test (parts A and B) and the forward and backward digit span test did not differ between groups at the end of month 6.

In terms of P300 latency (at the Cz, Pz, and Fz electrodes), the dementia (test) group exhibited significant shortening at month 6 ( $p=0.05$ ,  $p=0.03$ , and  $p=0.03$ , respectively). In the control group, however, the increase was not significant. The P300 amplitude did not differ between groups at the end of month 6. All data are summarized in (Table 2). Pre- and post-treatment P300 traces from a dementia patient are shown in Figures 1 and 2 respectively.

At the end of treatment, a slight increase was evident in the UPDRS tremor subscale score of the de-

mentia group, but this was not significant ( $p<0.08$ ). No significant change was evident between pre-and post-treatment MRCP measurements of dementia patients following rivastigmine treatment. A significant decrease was evident only in the amplitude of the readiness potential of control patients. No significant change was evident when any other between-group pair of parameters was compared. No significant between-group difference was observed, at either month 0 or 6, in RT measurements. Changes in MRCP C3 electrode data and RT results are shown in Table 3. The MRCP trace of a dementia patient and the RT trace are shown in Figures 3 and 4.

Table 2. P300 results

	0. month		6. month		p value
	PDD	PD	PDD	PD	
Fz- latency (ms)	390 ± 38,8	358 ± 36,6	366 ± 31,1	363 ± 28,8	0,05-0,17
Cz- latency (ms)	390 ± 39,6	356 ± 35,8	363 ± 35,9	366 ± 29,9	0,03-0,18
Pz- latency (ms)	397 ± 40,6	351 ± 36,8	367 ± 32	371 ± 26,4	0,03-0,61
Fz-amplitude (µV)	10,6 ± 6,4	13,1 ± 7,7	15,4 ± 6,3	13,1 ± 3,8	0,88-0,19
Cz-amplitude (µV)	12,8 ± 4,1	14,6 ± 7	14,8 ± 6,8	15,5 ± 6,3	0,67-0,48
Pz-amplitude (µV)	12,2 ± 3	13,2 ± 6,5	13,8 ± 3,9	15 ± 6,1	0,39-0,33

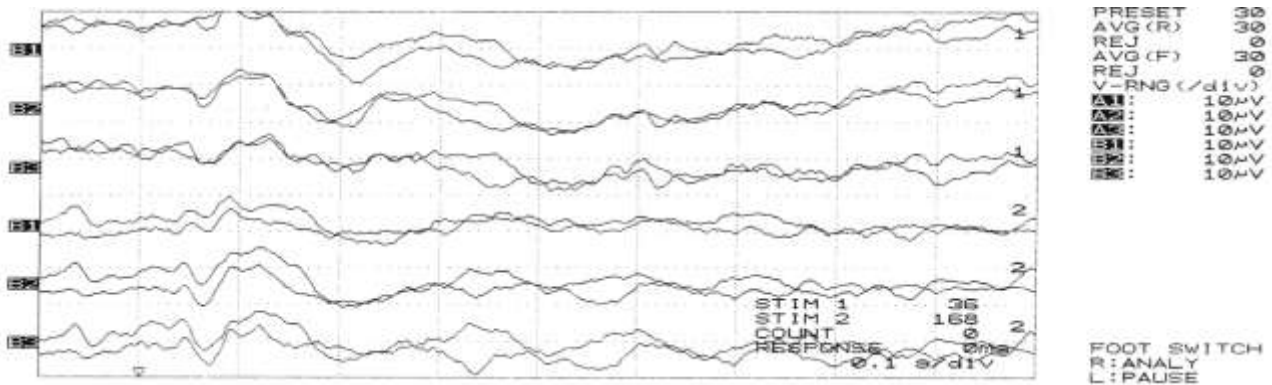


Figure 1

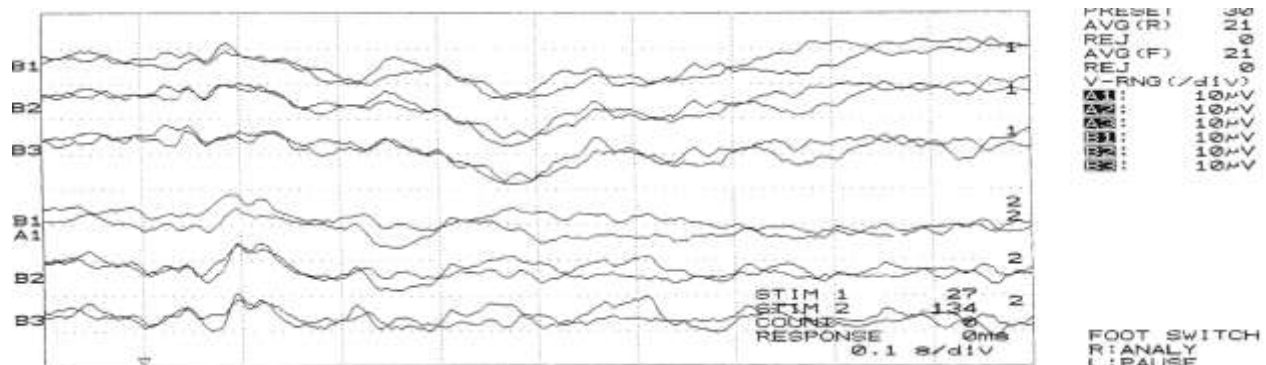


Figure 2

Table 3. Changes in MRCP C3 electrode data and RT results

	0. month		6. month		p value
	PDD	PD	PDD	PD	
RP latency (ms)	2450 ± 413	2580 ± 423	2597 ± 209	2547 ± 363	0,23-0,20
RP peak latency (ms)	2562 ± 666	2815 ± 562	2707 ± 182	2695 ± 335	0,31-0,67
RPAmplitude (µV)	22 ± 8	13 ± 9	25 ± 14	12 ± 10	0,09-0,02
RT (ms)	323 ± 85	291 ± 118	285 ± 88	322 ± 95	0,17-0,37

RP: Readiness Potential, RT: Reaction Time

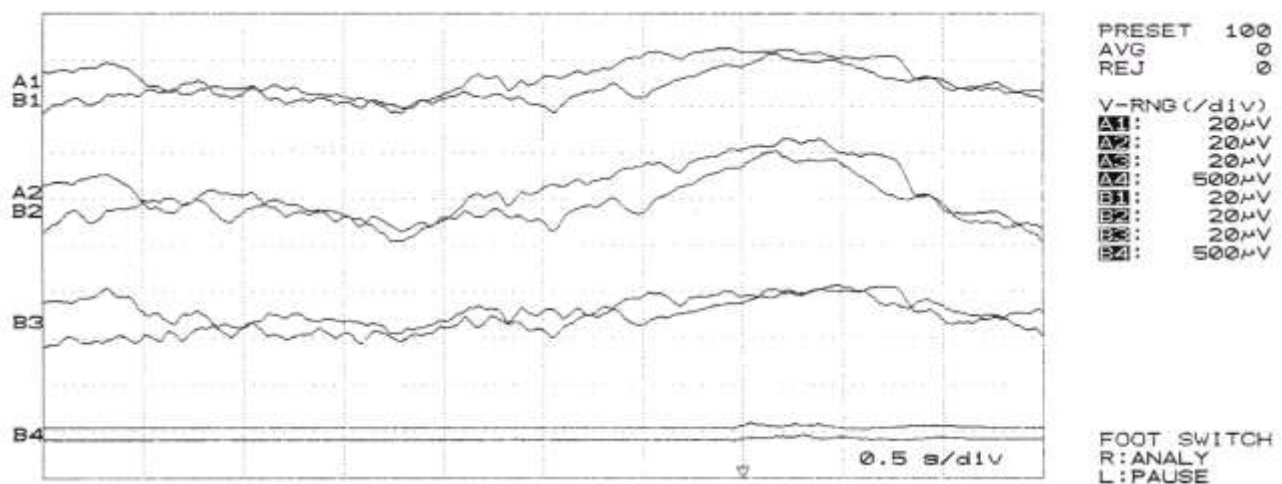


Figure 3

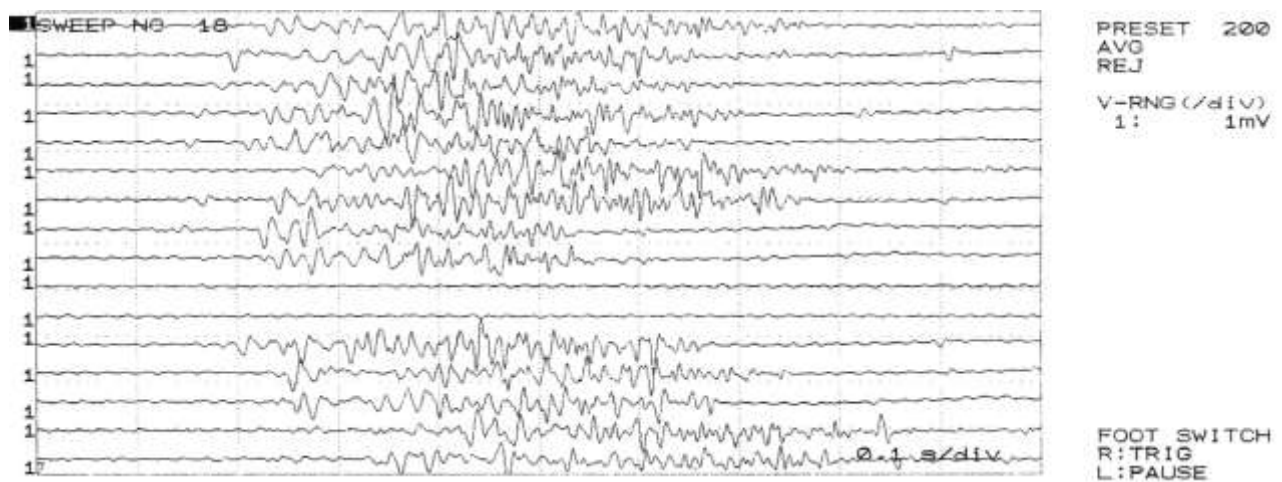


Figure 4

**DISCUSSION**

We sought to demonstrate neurophysiologically an influence of rivastigmine, used to treat PDD, on cognitive functioning. We also explored, again neurophysiologically, whether motor functions (tremor and bradykinesia) would deteriorate over the course of treatment. We found that comparisons of neuropsychological test data obtained before and after rivastigmine treatment

showed improvement, associated with reduced P300 latency (an objective indication of cognitive functioning). The MRCP and RT test results showed that motor findings did not deteriorate significantly during treatment.

Previous epidemiological studies assessing the risk of PDD found that the risk of dementia increased with advanced age (regardless of age at disease onset) (10); a low level of education (9); long duration of disease;

and the severity of disease symptoms (11). The average ages of the patients in our two groups were similar, as were their educational levels. However, the PD duration of the dementia group was longer than that of the control group. It must be remembered, however, that our reason for inclusion of PD patients without dementia was, first, to assess whether their motor functions would deteriorate by the end of month 6 in the absence of rivastigmine therapy. Our other purposes were to assess whether regression in cognitive functioning would occur over the 6-month period, attributable to the degenerative nature of PD; and to observe whether the P300 latency would become extended. We did not wish to compare between-group differences in the effects of the drug, but rather to neurophysiologically evaluate the natural 6-month disease course of each control patient. We are thus of the view that the difference in PD duration between the two groups did not influence our results.

No significant difference in IADL scores before or after treatment was evident in the dementia group. Although the absence of any influence of such improvement on functional capacity may be attributable to the short follow-up duration. The IADL is relatively less effective than other tests evaluating daily life activities and may have failed to reveal the effectiveness of treatment. We consider that such effectiveness could be rendered more visible by employing scales that evaluate daily life activities in more detail.

The prevalence of depression was 9% in PD and 13% in PDD patients (12). In our control group, depression was considerably more prevalent than in PDD patients. This may be attributable to our study design, because the Geriatric Depression Scale (GDS) was used. Using a GDS scale, patients who scored 15 points or over were excluded from the study. This might explain why fewer patients with depression were evident in the dementia group.

The prevalence of hallucinations in PD patients ranges from 25% to 40% and from 45% to 65% in PDD patients (13). It has been suggested that visual hallucinations are precursors of dementia (14, 15). One of the nine patients in our dementia group reported visual hallucinations, but no hallucinations were reported in the control group. The frequency of hallucinations in the single dementia patient mentioned was reduced following rivastigmine treatment.

In PDD patients, attention and executive functions are primarily affected (16). PDD patients exhibited significant impairment (compared to controls) in the digit span test and also in the trail-making test. Although slight improvements were evident after rivastigmine therapy, these were not significant. It may be that our sample size was too small to allow improvements to be detected; this is a limitation of our study.

When executive functioning was evaluated, the test group was significantly more impaired than the control group. Although a slight improvement was evident

after rivastigmine therapy, this was not significant. In the control group, however, such functioning deteriorated over the 6 months. This may be attributable to the degenerative process of PD. Thus, when the two groups were compared, it appeared that rivastigmine stopped such deterioration. Previous studies on rivastigmine also showed that the drug improved executive functioning (7, 17).

A general overview of neuropsychological test results revealed significant differences between the dementia and control groups in all of memory, attention, and executive functioning, and that improvement in the dementia group following treatment was limited to memory features only. It might be argued that rivastigmine significantly improves memory by exerting a cholinergic influence but fails to markedly improve executive functioning, considering that deficits in the mesocortical and nigrostriatal pathways are more prominent than are cholinergic deficits in terms of the pathogenesis of executive functioning.

The P300 latency is extended in patients with AD and those with mild forms of cognitive disease, compared to normal controls (3-6). The test has also been used to evaluate the effectiveness of AD treatment, because impairment in cognitive functioning has been correlated with impairment evident in the P300 test, and the P300 latency decreased with improvement in cognitive functioning evident by week 24 of drug treatment (6, 18). In many previous studies, comparisons of PD and normal control patients have shown that P300 latency was greater in PD patients (19). Although the presence and type of dementia in PDD patients can be determined using clinical and neuropsychological tests, the presence and (to an extent) the severity of dementia may also be assessed using the P300 test, which is an electrophysiological method of evaluation (4). Studies comparing P300 latencies in PDD and PD patients have shown that the PDD groups exhibited extensions of latency (20, 21). The P300 test has been used to evaluate the effectiveness of AD treatment, but has not been previously employed to evaluate the effectiveness of PDD treatment. In (control) PD patients without dementia, a slight increase in P300 latency was evident at 6 months, but PDD patients who underwent 6 months of rivastigmine therapy exhibited a statistically significant shortening of latency compared to the baseline value. Our findings are important both because, as shown previously, the P300 latency was extended in PDD patients; because this parameter may be objectively used during follow-up and to monitor drug effectiveness; and because latency was decreased by treatment.

The principal side-effect of rivastigmine was an increase in tremor in most PD patients, but the drug did not significantly aggravate bradykinesia or rigidity (7, 8, 22). In the present study, the MRCP and RT tests were used to this end. MRCP variations in PD patients parallel clinical exacerbation of the disease (23). In our present study, no significant change at 6 months, in

either the latency or amplitude of the readiness potential, was evident in either the control or dementia group, suggesting that motor functions (especially, bradykinesia) were not aggravated after rivastigmine therapy.

The RT test has been used to monitor motor slowdown in untreated compared to treated groups (24). In the dementia group, a non-significant improvement was observed, suggesting that attention was mildly improved by rivastigmine therapy. Attention is of

greater concern in PDD than AD patients. We also showed that no side-effect of motor slowdown was attributable to the drug.

This study had limitation. It examined a relatively small number of subjects. It is necessary increasing the number of patients to expand the study of.

Our study supports the notion that rivastigmine improves cognitive functioning in PDD patients, as assessed both clinically and electrophysiologically, and the drug did not adversely affect motor functioning.

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