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Evaluation of the Effect of Modafinil on Cognitive Functions in Patients with Idiopathic Hypersomnia with P300

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Background: Modafinil is a well-tolerated psychostimulant drug with low addictive potential that is used to treat patients with narcolepsy and other excessive sleepiness. Whereas favorable effects of modafinil on cognitive functions have been shown in a large number of studies, there are very few reports presenting the effects of modafinil electrophysiologically. The aim of this study was to investigate the effects of modafinil on auditory P300 latency and amplitude electrophysiologically.

Material/Methods: Eighteen patients (age range: 16–48 years) with a diagnosis of idiopathic hypersomnia (IH) were included in the present study. As a standard treatment, 200 mg/day modafinil was administered to each patient. The P300 auditory test was performed for each patient before and at the end of 1 week of modafinil treatment.

Results: After 1 week of modafinil treatment, mean P300 latencies (at all electrode sites) were significantly lower than the latencies before the treatment (*P* values for Fz, Cz and Pz recording sites were 0.039, 0.002, and 0.004, respectively). An increase in the P300 amplitudes was detected only at the Fz recording site, but not at Cz or Pz recording sites (*P* values for Fz, Cz, and Pz recording sites were 0.014, 0.100, and 0.05, respectively).

Conclusions: One week of modafinil treatment improved the cognitive performance, alertness, and executive functions in IH patients. Our electrophysiologically obtained findings provide further confirmation for previous reports in which modafinil has been shown to exert favorable effects on cognitive performance, alertness, and executive functions.

MeSH Keywords: Cognitive Reserve • Event-Related Potentials, P300 • Hypersomnolence, Idiopathic

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Background

Idiopathic hypersomnia (IH) is characterized by chronic, daily, excessive daytime sleepiness despite normal sleep. Excessive daytime sleepiness (EDS) has been linked to several conditions, including sleep deprivation, use of drugs or psychoactive substances, psychiatric or medical disorders, respiratory problems (such as obstructive sleep apnea), and structural lesions (such as stroke or head injury) [1]. Since it has been distinguished from narcolepsy, IH has been defined based on small cases series, with a variety of clinical forms [2]. IH patients have decreased wakefulness and increased naps during the day. Patients may also have prolonged difficulty in waking with automatic behavior, as well as confusion and repeated returns to sleep, a symptom named "sleep drunkenness". IH was identified relatively recently by Bedric Roth. He described patients not only with EDS *per se* (monosymptomatic) but also with prolonged night sleep who exhibit sleep drunkenness on waking (polysymptomatic) [3].

The 2nd edition of the International Classification of Sleep Disorders (ICSD-2) defines IH with long sleep time (LST) and IH without long sleep time (w/o LST). According to the ICSD-2, diagnosis of these hypersomnias can only be made when patients have both subjective excessive daytime sleepiness occurring almost daily for at least 3 months and a mean sleep latency of less than 8 min on the Multiple Sleep Latency Test (MSLT). A diagnosis of IH with LST requires prolonged nocturnal sleep time (more than 10 h) documented by interviews, actigraphy and/or sleep logs, great difficulty waking up either in the morning or at the end of a nap, and less than 2 sleep-onset rapid eye movements. In contrast, patients with IH w/o LST have normal nocturnal sleep (greater than 6 h but less than 10 h) [4]. Although cognitive insufficiency has not been reported in IH, concentration difficulty, distractibility, and momentary memory problems may be expected [5].

Modafinil, a 2-[(diphenyl methyl) sulfinyl] acetamide derivative (also known as Provigil or Modiodal), has recently been introduced for the treatment of excessive sleepiness associated with narcolepsy [6]. Although the exact mechanism of action is unknown, it appears that modafinil promotes vigilance by indirect activation of the frontal cortex via the hypothalamus and/or the tuberomammillary nucleus [7–9]. It may also inhibit dopamine-like receptors and GABA release [10–15]. Moreover, modafinil action has also been associated with increased glutamatergic, adrenergic, and histaminergic activity [16]. Hence, although modafinil has been studied in a very limited number of studies, use of modafinil for IH treatment has been increasing recently. This increased research interest is occurring because modafinil has recently been demonstrated to increase thalamocortical activity and cognitive functions, and to have favorable effects on attention, memory, and learning [17–25].

Event-related potentials (ERP) are cerebral responses associated with various psychological events or cognitive functions such as recognition of certain stimuli, and an objective parameter reflecting cognitive functions [26–28]. Previous studies have shown that, while P300 latency measures evaluation speed of a given stimulus, amplitude measures working memory functions [28–30]. Among ERP, auditory P300 is the most used for measured electrophysiologically cognitive functions. P300 is one of the most prominent positive peaks, occurring around 300 ms after the infrequently presented to respond by a certain task in the 'odd-ball paradigm' [31]. Particularly event related potentials which are a good indicator of cognitive function, are useful for analysis of brain physiology during cognitive function, and provide information about temporal function. Although in many studies, alterations in the P300 latency and amplitude have been demonstrated in neurological and psychiatric diseases, the effects of a cortex activating agent, modafinil, on P300 has not been investigated electrophysiologically yet [22,32–38].

Whereas positive effect of modafinil on cognitive functions has been shown in many studies, there are very few reports presenting the effects of modafinil electrophysiologically [17–24]. Therefore, we sought to investigate the effects of modafinil on P300 latency and amplitude electrophysiologically in patients who were diagnosed as IH clinically and for whom modafinil treatment has been initiated.

Material and Methods

Patient selection

We identified patients who admitted to our neurology or psychiatry outpatient clinics at Afyon Kocatepe University Medical Faculty, January 2010 to June 2011, diagnosed with IH, and in whom modafinil treatment was initiated. Among them, 18 patients who decided to participate in the study were included. All patients were fully informed about the purpose of the study and the procedures to be employed. All patients were asked not to use any other medication that may affect their cognitive functions except modafinil during the study period of 1 week. We excluded patients with mental retardation, hearing problems, any history of substance abuse or alcohol addiction that would prevent them from taking the test. The study protocol was approved by the Ethics Committee of Afyon Kocatepe University, and all patients participated voluntarily with written informed consent.

ERP recording techniques

Initially, baseline auditory ERPs were recorded in patients with IH. Then, the same test was repeated after 1 week of modafinil

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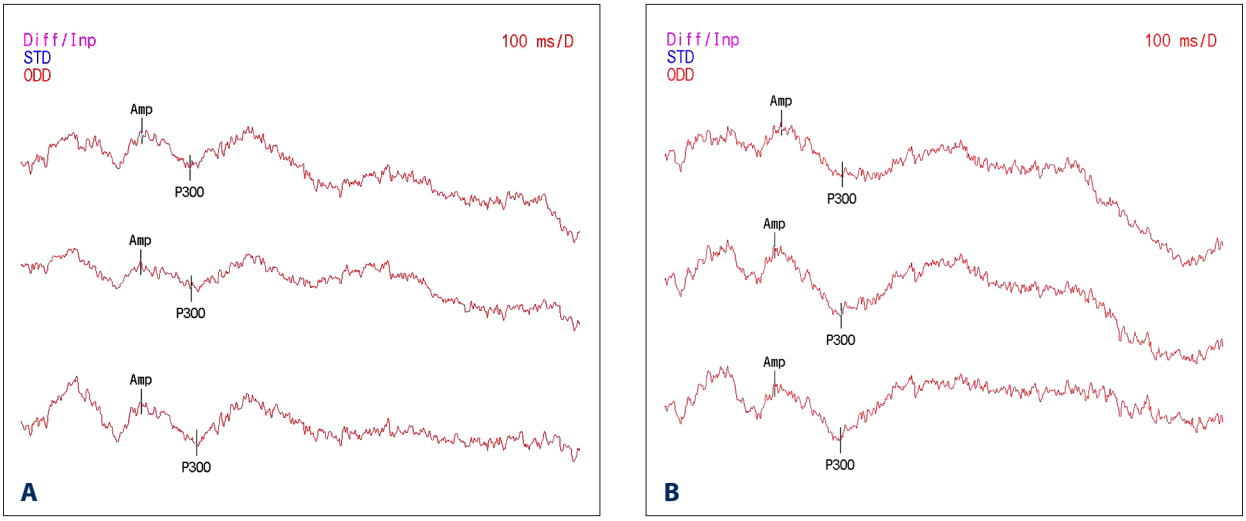

Figure 1. Samples of auditory P300 for before (**A**) and after (**B**) modafinil treatment.

treatment. Reproducibility and reliability of the P300 latency measurements have been clearly established by short- and long-term studies in normal controls after repeated recordings. On each session, P300 amplitude and latency were measured. In all patients, the P300 recordings were obtained after an optimal overnight sleep before the breakfast (at 9:00 am). All measurements were performed by the same electrophysiologist at the Department of Neurology, who was blinded to patient treatment status.

Recording conditions

Electroencephalographic (EEG) activity was recorded at the frontal (Fz), central (Cz), and parietal (Pz) electrode sites of the 10/20 international system using Ag/AgCl electrodes, affixed with electrode paste and tape, with an impedance of 10 k Ohm or less. The reference electrode was attached to the right earlobe and the ground electrode was attached to the left earlobe.

Stimulus set-up

In this study, Keypoint G4 workstation equipment (Denmark) auditory oddball stimulus set-up was used. A standard stimulus of 90 dB SPL intensity and 1000 Hz, and a target stimulus of 90dB SPL intensity and 2000 Hz frequency pure sound were used. Target stimuli constituted of 20% (n=60) of 300 total stimuli and were given in between standard stimuli in a random manner. Patients were asked not to move, not to talk, not to blink too much, and to look at a fixed point in the middle of the computer screen. They were asked to press the button whenever they heard random target stimuli applied in between the auditory stimuli.

Procedure

Prior to experimental procedures, a 5-min adaptation period was given for the patient and EEG was calibrated. Following the attachment of electrodes, patients were placed on an adjustable chair in an isolated room adjacent to the recording room. Subjects were instructed to sit quietly with open eyes, follow the stimuli carefully, and to try to determine rare tones of 1000 Hz frequency. The amplitudes were measured peak-to-peak. The amplitude and latency measurements were compared before and after 1 week of modafinil treatment.

Statistical methods

Statistical analysis was performed by using SPSS 10.0 software for Windows. All data are presented as mean ±S.D. The Wilcoxon test and paired t-test were used for the statistical analysis. $P<0.05$ was considered significant.

Results

In total, 18 patients were evaluated in the study (8 males, 10 females). Mean age was 23.0±6.7 (min: 16, max: 48). The grand means of the auditory P300 at all electrode sites for the 2 time-points (before and after treatment) are presented in Figure 1. The latencies of the P300 component measured at the Fz, Cz, and Pz electrode sites were assessed separately. After 1 week of modafinil treatment, mean P300 latencies (at all electrode sites) had decreased significantly compared to latencies before the treatment (*P* values 0.039, 0.002, and 0.004, respectively, Table 1). After 1 week of modafinil treatment but mean P300 amplitudes were increased. A significant increase at the Fz electrode was detected after 1 week of modafinil treatment but mean P300 amplitudes were decreased and a significant increase at the Fz electrode was detected (Fz: 0.014, Cz: 0.100 and Pz: 0.05, Table 1).

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Table 1. Fz, Cz and Pz latency and amplitude values in 18 patients with diagnosis of IH, before and after 1 week of modafinil treatment.

	Before modafinil	After 1 week treatment of modafinil	P value
Fz latency (ms)	331.4±19.1	314.1±28.5	**0.039**
Fz amplitude (μV)	14.9±8.30	20.8±13.1	**0.014**
Cz latency	335.6±15.2	311.77±27.7	**0.002**
Cz amplitude	16.36±7.47	21.3±9.27	0.100
Pz latency	334.9±14.8	312.0±26.0	**0.004**
Pz amplitude	15.6±7.79	21.1±11.6	0.050

ms – milliseconds; μV – microvolt.

Discussion

This study shows that treatment with modafinil (200 mg/day) has positive effects on auditory P300. We observed a shortening of P300 latency at Fz, Cz, and Pz sites after 1 week of modafinil treatment compared to pre-treatment. Moreover, an increase only at the Fz site was detected at the P300 amplitudes of the same sites and there was no amplitude change at the Cz and Pz sites. In line with earlier reports, our results show that modafinil has positive effects on cognitive functions. P300 ERP application (particularly P300 ERP latency) is a well-established neurophysiological approach in any disease where cognitive functions are impaired [39]. Our method is relatively simple, safe, non-invasive, and reproducible compared to other metabolic and structural studies of the brain. P300 latency has been related to the speed of stimulus evaluation [40]. Moreover, P300 latency has been reported to exhibit a good correlation with the conventional neurophysiological tests (e.g., the Wechsler Adult Intelligence Scale score and Wechsler memory scale) for the assessment of cognitive performance [41–43]. The effects of modafinil on cognitive functions have been explored in a number of earlier studies. Although P300 latency is a test that is widely used for the evaluation of cognitive performance in many diseases, the effect of modafinil on P300 latency and amplitude has been investigated in very few studies [44].

In an earlier animal study, Shuman et al. showed the effects of modafinil on 3 types of memory (spatial memory, context fear memory, and cued fear memory) and found specific enhancements of hippocampus-dependent spatial memory and contextual fear memory. They found that the effect of modafinil on memory is similar to other conventional psychostimulants, but is more specific on hippocampus-dependent memory [45]. Similarly, in a placebo controlled, double-blind study on healthy young volunteers, Natalie et al. demonstrated that 200 mg of modafinil facilitated rapid shifts of attention [23]. An extensive studies performed in this field was by Wesensten et al., who showed that modafinil at a dose of 200 mg/day significantly improved performance in verbal fluency, flexibility, and originality compared to placebo as measured by the Torrence Test of Creative Thinking-Verbal. Furthermore, they found that modafinil also improved performance in the Wisconsin Card Sorting Test (which measures executive function) and Haylings Sentence Completion (which measures the ability to inhibit verbal responses) [46]. In a 2002 study, the same group demonstrated that modafinil at the doses of 200 mg and 400 mg significantly improved the cognitive performance and alertness compared to placebo, at a similar level to 600 mg of caffeine, in people who were subjected to sleep deprivation [47]. Muller et al. evaluated the effects of modafinil 200 mg versus placebo on a numeric working memory task, a delayed matching-to-sample task, letter cancellation, and trail-making using a double-blind crossover design. Modafinil decreased errors on the numeric working memory task, particularly for the most difficult condition [19]. In addition, Turner et al. showed that modafinil increased higher-order performance in non-sleep-deprived volunteers [48]. In general, the above-mentioned and similar studies clearly present the beneficial effect of modafinil on alertness, cognitive performance, and memory. However, in some other studies a similar effect was not observed for modafinil. For example, Randall et al. found that modafinil was not superior over placebo in tests of long-term memory, executive function, visuospatial and constructional ability, or category fluency. In that study, the authors reported that the effect of modafinil on the improvement of cognitive performance is limited in non-sleep-deprived subjects [49]. Similarly, in a study on 18 healthy non-sleep-deprived adults, Baransky et al. emphasized that modafinil's effect on cognitive performance was not as expected, and they suggested further investigation [22].

Based on our data, we found that 200 mg/day of modafinil treatment for a period of 1 week had positive effects on cognitive performance, alertness, and executive function. Our results are in accordance with previous reports on the effect of

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modafinil on cognitive functions and alertness. The mechanism of action of modafinil remains controversial. Data from animal experiments suggests that modafinil may exert its effect by direct activation of the tuberomammillary nucleus and the hypocretin neurons of the perifornical area [50]. Currently, an indirect stimulation by noradrenaline (particularly, via α_1-adrenoreceptor) and other arousal-enhancing neurotransmitters (e.g., serotonin, histamine, and acetylcholine) seems to be the most likely mechanism of action of modafinil [51,52]. Some researchers also found that glutamate increases and GABA inhibits the effects of modafinil [15]. When all these effects of modafinil are considered together, it would not be a surprise that it has a shortening effect on P300 latency and increasing effect on Fz P300 amplitude at all 3 sites (Fz, Cz, and Pz) and it increases cognitive performance, alertness, and executive functions. In earlier animal studies, modafinil has been shown to increase thalamocortical activity [17]. Joo et al. found that single-dose modafinil in healthy non-sleep-deprived volunteers increases cerebral blood flow in the thalamus, brainstem, insular cortex, and limbic system, which are related to arousal, attention, executive function, and emotional functions, respectively [53].

Conclusions

This study demonstrates that 1 week of modafinil treatment causes a shortening of P300 latency at all 3 sites (Fz, Cz, and Pz) and increases Fz P300 amplitude in patients with IH. This result is an electrophysiological confirmation of previous studies in which modafinil has been shown to improve cognitive performance, alertness, and executive functions. This study is one of the first in this field, and needs to be confirmed with neuropsychological tests and more subjects.

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