Modafinil in Obstructive Sleep Apnea-Hypopnea Syndrome: A Pilot Study in 6 Patients

Key Words
Pharmacological treatment
Obstructive sleep apnea-hypopnea syndrome
Excessive daytime sleepiness

Abstract
We studied the effects of modafinil, a vigilance-enhancing drug, on excessive daytime sleepiness, memory, night sleep and respiration in 6 patients with obstructive sleep apnea-hypopnea syndrome (OSAHS) using a double-blind random cross-over design with 24-hour polysomnography, verbal memory test and a 5-week sleep-wake diary kept by the patients. There were two 2-week treatment periods in which either modafinil or placebo was used; they were separated by a 1-week wash-out period. Our results show that modafinil reduces daytime sleep duration, lengthens the duration of subjective daytime vigilance and improves long-term memory in patients with OSAHS without modifying night sleep and respiration events.

Introduction
In the obstructive sleep apnea-hypopnea syndrome (OSAHS), periodic obstructions of the upper airways deteriorate sleep and lead to daytime sleepiness, impaired cognitive performance and a high risk of traffic accidents [1, 2]. Therapy focuses on the relief of upper airway obstruction by nasal continuous positive airway pressure (CPAP), but compliance to treatment varies from 50 to 85% [3]. An approach to symptomatic treatment aimed at reversing the neuropsychological sequelae of sleep apneas by conventional stimulants, such as amphetamines, is limited by the potential sympathomimetic effect of these drugs in sensitive OSAHS patients. Modafinil (Modiodal®, Laboratoire Lafon, Maison-Alfort, France), a new putative α1-adrenergic postsynaptic potentiatior, is a non-amphetamine vigilance-enhancing drug [4], devoid of peripheral effects. In normal subjects, modafinil enhances vigilance measured by multiple sleep latency tests after a normal night sleep [5] and reverses both sleepiness [6] and cognitive impairment [7] after sleep deprivation. Its efficacy against daytime sleepiness in patients with narcolepsy or idiopathic hypersomnia has been demonstrated [8, 9]. The drug has a 1- to 4-hour peak serum concentration after oral administration and a 10- to 13-hour half-life [10]. We report a pilot study (6 OSAHS patients) of tolerance and efficacy of modafinil in the treatment of daytime sleepiness and memory.

Material and Methods
We performed a random placebo-controlled double-blind crossover study in 6 male OSAHS patients aged 49–69. They reported excessive daytime sleepiness (more than one sleep attack a day in the sleep diary), had a mean apnea-hypopnea index of 38 ± 24, minimal SaO₂ of 86 ± 6% and a body mass index of 27 ± 3 kg/m². Over a 5-week period, patients underwent 2 weeks of modafinil or placebo 100 mg twice a day (at 9 a.m. and noon), 1 wash-out week and 2
weeks of placebo or modafinil. Tolerance was assessed at the end of each treatment session by interrogation, clinical examination, measuring of weight and blood pressure and a 24-hour electrocardiogram. The efficacy of the drug on daytime sleepiness, night sleep and memory was assessed subjectively and objectively. The patients kept a diary of daytime sleep attacks, yawning, daytime alert wake and sleep duration as well as quality of sleep for 5 weeks [11]. On the other hand, a verbal memory test [12] and a 24-hour polysomnogram (PSG) were performed at the end of each treatment period: patients stayed in bed for 24 h except for meals and voiding, but were otherwise free to do what they liked, from 10 a.m. to 10 p.m. (daytime) and 10 p.m. to 10 a.m. (nighttime). The recordings were made with a ECEM 16-channel polygraph (ECEM alpha, Vickers Medical SA, France) and a Biox-Ommeda oximeter (Biox 3740, Ohmeda Ltd, Co, USA) and included an electroencephalogram, an electromyogram, an electro-oculogram, oxygen saturation, an electrocardiogram, nasal thermistors and thoracic and abdominal respiratory movements. Sleep staging was scored visually according to the criteria of Rechtschaffen and Kales [13], and microarousals were defined according to the criteria of Bonnet et al. [14]. Results were analysed with Wilcoxon's rank tests using Statview 4.1 software (Abacus Concepts, Inc., Calif., USA). The study was approved by the local ethics committee.

Results

Drug tolerance was good, and no patient stopped the treatment during the study. One subject has a mild supine blood pressure increase from 140 mm Hg under placebo to 170 mm Hg under modafinil. No differences were found between modafinil and placebo in cardiac frequency, R-R interval and body weight. There was no report of cardiac arrhythmia under modafinil.

There were no differences between placebo and modafinil in any of the night-sleep-related events such as total sleep time, slow-wave and rapid eye movement sleep durations and percentages, sleep efficiency or latencies for any stages during the night PSG. Nor was there a difference in sleep fragmentation (number of microarousals, related or not to apneas and hypopneas), the apnea-hypopnea index (during the day and at night) or in minimal SaO₂.

In contrast, the day PSG showed a 42% reduction in daytime sleep duration (mean ± SD) (modafinil: 45 ± 36 min; placebo: 77 ± 41 min; p < 0.05) (fig. 1), essentially due to a reduction of 52% in sleep stage 2 (modafinil: 25 ± 19 min; placebo: 53 ± 31 min; p < 0.03). No drug order effect was seen. Similarly, the analysis of the sleep-wake diaries showed that the duration of alert wake without yawns or naps during daytime increased by 1 hour (modafinil: 18.7 ± 1.2 h; placebo: 17.7 ± 1.2 h; p < 0.01) with no change in the number of sleep attacks and yawning. Five of the 6 subjects preferred the modafinil period.

Memory test results were similar to those of the age-matched reference population. In all subjects, delayed free recall improved (modafinil: 14.8 ± 0.8; placebo: 12.8 ± 1.3; p < 0.05; maximal possible score was 16), but there were not differences in total immediate free and cued recall and recognition.

Discussion

This pilot study of the effect of modafinil in OSAHS shows that the drug reduces daytime sleep duration and improves the duration of alert wake and long-term memory in patients with OSAHS without modifying night sleep and respiratory events. The drug was devoid of any significant adverse effects.

Memory impairment in OSAHS has been related to night hypoxia and daytime sleepiness [15]. Under modafinil, our patients reached supernormal scores, but there was no difference in night hypoxia. On the other hand, modafinil improves short-term memory performances in sleep-deprived volunteers [6]. Thus, the reduction in sleepiness in our OSAHS patients could have improved long-term memory under modafinil.

Daytime sleepiness is the key symptom of OSAHS, and its mechanism remains unclear, though it is not always related to night microarousals or hypoxemia [16].
and may persist in spite of a correct treatment of apnea [1]. Here, 5 subjects of 6 experienced a reduction in their sleepiness as measured by daytime sleep duration. This effect is hardly comparable to that of CPAP treatment, since we used a continuous 24-hour polysomnography paradigm to assess sleepiness. In the assessment of sleepiness under CPAP treatment, multiple sleep latency tests have been used, but they evidenced only minor changes [1]. It has been reported that modafinil reduces sleepiness in normal sleep-deprived subjects and in patients with daytime somnolence [5–8]. Here, modafinil did not suppress but significantly decreased daytime sleep duration and lengthened the duration of waking time. Moreover, under modafinil, the duration of daytime sleep was similar to standard values observed in normal subjects recorded under the same conditions [17]. This suggests that pharmacological agents can partially reverse the deleterious consequences of the disease.

This preliminary study suggests that modafinil may have a part in therapeutic strategy of OSAHS. Since it had no effect on nighttime respiratory events, its position as a sole or a complementary treatment of residual sleepiness under CPAP treatment remains to be established in the long term.

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References


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