Available online at www.sciencedirect.com
ScienceDirect
Progress in Neuro-Psychopharmacology & Biological Psychiatry 32 (2008) 552–559
Progress In Neuro-Psychopharmacology & Biological Psychiatry
www.elsevier.com/locate/pnpbp

Placebo and modafinil effect on sleepiness in obstructive sleep apnea ☆

Lia Rita A. Bittencourt [a,*], Ligia M. Lucchesi [a], Adriana D. Rueda [a], Silvério A. Garbuio [a], Luciana O. Palombini [a], Christian Guilleminault [b], Sergio Tufik [a]

[a] *Sleep Medicine and Biology Discipline, Psychobiology Department, Universidade Federal de São Paulo, Napoleão de Barros 925, São Paulo 04024-002, SP Brazil*
[b] *Stanford University Sleep Disorders Center, Suite 3301, 401 Quarry Road, Stanford, CA 94305, USA*

Received 2 August 2007; received in revised form 19 October 2007; accepted 20 October 2007
Available online 30 October 2007

Abstract

Introduction: Previous studies have evaluated the effect of modafinil on residual excessive daytime sleepiness (EDS) in patients with obstructive sleep apnea syndrome (OSAS) under effective CPAP treatment. Even though those trials also used placebo groups, we suppose that the placebo effect might influence the patients' response to modafinil.
Methods: Twenty sleepy patients with OSAS under CPAP treatment were selected. All of them had Epworth Sleepiness Scale (ESS) >10. Following baseline evaluation (T1), all subjects were instructed to take placebo for 7 days. After this single-blind placebo phase and second evaluation (T2), patients were randomly allocated to placebo or modafinil treatment for 21 days in a double-blind protocol. Patients underwent a final evaluation (T3) on the last day of drug intake. The evaluations at T1, T2 and T3 consisted of: medical and laboratory examinations, nocturnal polysomnography, ESS, maintenance of wakefulness test (MWT) and complex reaction time (CRT-NY). In addition, in T2 and T3 the change of illness severity scale (CGI-C) and the evaluation of quality of life (SF-36) were applied.
Results: The comparison between the two groups during the three periods studied, showed the following results: in the modafinil group, ESS score did not change during the initial placebo period, but there was a significant reduction during the modafinil treatment period ($p=0.0006$); in the placebo group a significant reduction occurred during the initial placebo period ($p=0.05$), and no further change was observed in the treatment (placebo) period. A significant difference was found between the two groups after the placebo period (T2) ($p=0.02$). Three patients (33%) of the modafinil group and 9 patients (81%) of the placebo group were classified as placebo-responsive (X^2: $p=0.039$). In the treatment period, reaction time was significantly reduced in the modafinil group compared to the placebo group ($p<0.02$). There was a trend toward improvement in overall clinical condition and also in some domains of SF-36 in the modafinil group.
Conclusion: In summary, our study confirms that modafinil used adjunctively with CPAP therapy improves subjective daytime sleepiness in patients with OSAS who were regular users of CPAP therapy but still experienced sleepiness. Moreover, it could help in the improvement of objective measures of behavioral alertness and reduce functional impairments. The usefulness of a blinded placebo period for systematic investigation of placebo role in studies based on subjective response is a point that should be considered in this type of drug trial.

Keywords: CPAP; Epworth Sleepiness Scale (ESS); Modafinil; Obstructive sleep apnea syndrome (OSAS); Placebo effect; Residual sleepiness

Abbreviations: AASM, American Academy of Sleep Medicine; AHI, Apnea/Hypopnea Index; CGI-C, Clinical Global Impression; CPAP, Continuous Positive Airway Pressure; CRT-NY, Complex Reaction Time; DBP, Diastolic Blood Pressure; EDS, Excessive Daytime Sleepiness; ESS, Epworth Sleepiness Scale; FOSQ, Functional Outcomes of Sleep Questionnaire; MWT, Maintenance of Wakefulness Test; OSAS, Obstructive Sleep Apnea Syndrome; PSG, Polysomnography; SBP, Systolic Blood Pressure; SD, Standard Deviation; SE, Side Effects; SF-36, Short-Form Health Survey; UNIFESP, Universidade Federal de São Paulo.

☆ Supported/Funding: Associação Fundo de Incentivo à Psicofarmacologia (AFIP); Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP)-CEPID; Laboratoire Lafon.

* Corresponding author. Rua Napoleão de Barros, 925, Vila Clementino-04024-002, São Paulo, Brazil. Tel.: +55 11 21490155; fax: +55 11 55725092.
E-mail address: lia@psicobio.epm.br (L.R.A. Bittencourt).

0278-5846/$ - see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.pnpbp.2007.10.016

1. Introduction

Obstructive sleep apnea syndrome (OSAS) is a relatively common condition and is estimated to affect 2 to 4% of middle-aged adults (Young et al., 2002). OSAS is a chronic disorder characterized by repeated episodes of complete or partial collapse of the upper airway during sleep. In most instances these episodes result in hypoxia and microarousals from sleep that last only seconds and patients are rarely aware of. The consequent sleep fragmentation leads to excessive daytime sleepiness (EDS) (AASM, 1999). Patients also complain of unrefreshing sleep and impairment in cognitive tasks such as concentration and memory (Endeshaw, 2006; Heitman and Flemons, 2001). The EDS caused by OSAS is one of the main features responsible for occupational and automobile accidents and also contributes to social engagement impairment (Krieger et al., 2002).

Continuous positive airway pressure (CPAP) is the treatment of choice for patients with OSAS and the most effective method to reduce EDS (Heitman and Flemons, 2001). However, some patients who are regular CPAP users continue to complain of residual EDS even when other causes of somnolence are ruled out (sleep deprivation, other sleep disorders, alcoohol and hypnotic drugs use) (Guilleminault and Philip, 1996).

Modafinil, a [2-(diphenyl-methyl)-sulfinyl-2 acetamide] derivative, is a central stimulant of post-synaptic alpha-1 adrenergic receptors (Ferraro et al., 1996a,b). Differently from amphetamines, this medication acts in more specific brain areas (Ferraro et al., 2000, 1999, 1996a,b; Scammell et al., 2000) and promotes an increase in the alertness in a selective way. Mood changes are infrequent and modafinil does not lead to sleep rebound seen with amphetamines after withdrawal. Treatment with modafinil has not shown development of dependence and tolerance (Jasinski, 2000; Jasinski and Kovacevic-Ristanovic, 2000).

The use of modafinil is currently established for narcolepsy and idiopathic hypersomnia (Beusterien et al., 1999; Guilleminault et al., 2000; Jasinski and Kovacevic-Ristanovic, 2000; Schwartz et al., 2003; US Modafinil in Narcolepsy Multicenter study group, 2000). In addition, studies involving patients with neurological, psychiatric and other disorders associated with fatigue and hypersomnolence also show benefits with this drug (Damian et al., 2001; Hogl et al., 2002; Rammohan et al., 2005; Talbot et al., 2003).

Studies with both animals (Panckeri et al., 1996) and humans with OSAS (Arnulf et al., 1997) using modafinil have demonstrated increase in vigilance without changes in the sleep pattern (US Modafinil in Narcolepsy Multicenter study group, 2000). One of the main concerns regarding the chronic use of amphetamine is the increase of cardiovascular side effects. The use of 300 mg modafinil in OSAS patients has shown only a discrete increase of blood pressure measurement after mental stress and physical exercise (Heitmann et al., 1999).

Previous studies have evaluated the effect of modafinil on residual EDS in OSAS patients under effective CPAP treatment (Black and Hirshkowitz, 2005; Dinges and Weaver, 2003; Kingshott et al., 2001; Pack et al., 2001; Schwartz et al., 2003). Some of them have found reduction of EDS only with objective tests (Kingshott et al., 2001), others with subjective tests (Schwartz et al., 2003) and others still with both tests (Black and Hirshkowitz, 2005; Pack et al., 2001; Roth et al., 2006). In spite of the use of placebo in parallel groups in these trials, we suppose that placebo effect could have persisted in modafinil groups after randomization and be responsible for these different results. In order to test our hypothesis, that is, the placebo effect during the use of modafinil, we submitted all patients to a placebo period before randomization (to drug and placebo groups).

2. Methods

2.1. Study design

This was a prospective, randomized, double-blind, parallel groups and placebo-controlled study conducted at the Universidade Federal de São Paulo (UNIFESP) with the approval of the local Ethical Committee. All participants provided written informed consent. The study included a 30-day screening period with CPAP therapy, a 7-day screening and baseline evaluation (T1). Following baseline evaluation, all subjects were instructed to take two placebo capsules at 8 AM and one placebo capsule at noon for 7 days. After this single-blind placebo phase and second evaluation (T2), patients were randomly allocated to placebo or modafinil treatment in a double-blind protocol with a similar schedule of drug intake (two capsules at 8 AM and one capsule at noon) for 21 days. Patients underwent a final evaluation (T3) on the last day of drug intake. The evaluations at T1, T2 and T3 consisted of: medical and laboratory examinations, nocturnal polysomnography, Epworth Sleepiness Scale (ESS), maintenance of wakefulness test (MWT) and complex reaction time (CRT-NY). In addition, in T2 and T3 the change of illness severity scale (CGI-C) and the evaluation of quality of life (SF-36) were applied (Fig. 1). Modafinil (100 mg) and identical-looking placebo were supplied by Lafon Laboratory. Each capsule of the active treatment contained 100 mg of modafinil. The total dose was 300 mg/daily.

2.2. Patient selection

During the screening period, 31 patients were attended, 09 did not meet the inclusion criteria during the protocol process.

Twenty two patients with OSAS and CPAP treatment were selected. The inclusion criteria were: age 18 to 65 years; baseline apnea/hypopnea index (AHI: number of apneas and hypopneas per hour of sleep) >15; regular users of CPAP (use of >5 h per night) for at least one consecutive month, before baseline evaluation (checked by built-in compliance meter). They were included in the study if AHI <5 on polysomnography with CPAP, demonstrating treatment efficacy. Patients' residual sleepiness was based on an ESS score >10.

Patients were excluded if they had: a sleep disorder other than OSAS or other diseases which cause EDS; uncontrolled arterial hypertension or any other cardiovascular disease;