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Brief Communication

Findings of the Maintenance of Wakefulness Test and its relationship with response to modafinil therapy for residual excessive daytime sleepiness in obstructive sleep apnea patients adequately treated with nasal continuous positive airway pressure

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ABSTRACT

Objective: We aimed to examine the relationship between subjective and objective sleepiness in obstructive sleep apnea syndrome (OSAS) patients with residual sleepiness, and to determine whether baseline objective sleepiness severity predicts the response to modafinil therapy.
Methods: Data were obtained from a randomized, placebo-controlled modafinil (200 mg/day) study in Japanese OSAS patients with residual sleepiness receiving nasal continuous positive pressure (n-CPAP) treatment. We analyzed 50 participants whose subjective (Epworth Sleepiness Scale [ESS] total score) and objective (Maintenance of Wakefulness Test [MWT] sleep latency) sleepiness were evaluated before and after treatment. Subjects were dichotomized into two subgroups according to the mean baseline MWT sleep latency. ESS total score and MWT sleep latency changes after treatment were compared between the placebo and modafinil groups in both subgroups.
Results: The mean baseline ESS total score and MWT sleep latency were 14.1 ± 2.8 and 14.2 ± 4.9 min, respectively; there was no significant correlation between these two variables. Patient characteristics were similar between the two subgroups (MWT sleep latency: <14 min, $n = 23$; ≥14 min, $n = 27$). In the <14-min subgroup, changes in ESS total score and MWT sleep latency after treatment were significantly greater in the modafinil group than in the placebo group ($p = 0.005$). In the ≥14-min subgroup, changes in these parameters did not differ between the treatment groups.
Conclusion: In OSAS patients with residual sleepiness, the objective sleepiness level was not as high as expected, despite increased subjective sleepiness. Improvements in subjective and objective sleepiness seemed difficult to achieve with modafinil treatment among subjects with less objective sleepiness.

1. Introduction

Obstructive sleep apnea syndrome (OSAS) is characterized by recurrent episodes of respiratory pause due to upper airway collapse during sleep. In moderate-to-severe OSAS cases, the risk of cardiovascular complications is likely to increase [1], and pathological daytime sleepiness may occur mainly because of marked fragmentation/disruption of nocturnal sleep [2]. Excessive daytime sleepiness (EDS) due to OSAS, which may lead to the occurrence of occupational and vehicular accidents [3–5], is mostly suppressed by adequate nasal continuous positive airway pressure (n-CPAP) therapy, by which the upper airway patency is maintained with positively pressured airflow delivered through a nasal mask during sleep [6]. However, in some OSAS cases, EDS persists despite adequate n-CPAP therapy [7,8]. In Europe and the United States, approximately >5% of OSAS patients receiving n-CPAP therapy have residual sleepiness [7]. Modafinil, a wakefulness-promoting agent, has been reported to alleviate residual sleepiness and to improve daytime functioning in such cases [9–12].

Most residual sleepiness cases have been diagnosed based only on subjective sleepiness. Furthermore, the levels of objective sleepiness measures in patients with residual sleepiness and the

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clinical characteristics in responders and nonresponders to modafinil treatment have not been confirmed. The present study aimed to examine the relationship between objective and subjective sleepiness, and to determine whether baseline objective sleepiness severity predicts the response to modafinil treatment for residual sleepiness in OSAS patients.

2. Methods

Data were obtained from a four-week, randomized, double-blind, placebo-controlled, parallel-group study (Study No. AFT-801-0305) using a fixed dose of modafinil (200 mg/day) in Japanese OSAS patients with residual sleepiness under adequate n-CPAP treatment. The Ethics Committee of the Neuropsychiatric Research Institute (Tokyo, Japan) approved this study. Patient eligibility criteria have been previously described [11].

In the present study, 50 patients who underwent the Maintenance of Wakefulness Test (MWT) and self-checked the Epworth Sleepiness Scale (ESS) before and four weeks after modafinil or placebo treatment were analyzed. The MWT is a polysomnographic measure of one's ability to remain awake in an environment with low levels of stimulation [13]. The ESS is a subjective sleepiness assessment score [14]. The MWT was applied in four sessions at 2-h intervals for a maximum of 20 min per session, as in previous studies [10,12].

Among the 114 subjects enrolled in the principal study, the homogeneity of patient characteristics was examined in the groups undergoing ($n = 50$; modafinil, $n = 22$; placebo, $n = 28$) and not undergoing ($n = 64$; modafinil, $n = 30$; placebo, $n = 34$) the MWT by comparing each characteristic parameter between the two groups. The patients' sex, age, body mass index (BMI), ESS score at baseline, and apnea–hypopnea index (AHI) during n-CPAP therapy were evaluated. A two-sample *t* test and Fisher exact test were used for numerical and categorical variables, respectively.

To examine the relationship between subjective and objective sleepiness in subjects with residual sleepiness, Pearson correlation coefficients were calculated for the mean MWT sleep latency and ESS total score at baseline and after administration of the investigational product. Thereafter, the 50 subjects who underwent the MWT were divided into two subgroups, namely, those with sleep latency at baseline equivalent to or over the mean value of the whole subjects, and those with that below the mean value. The patient characteristics of the two subgroups were compared using the two-sample *t* test for numerical variables and Fisher exact test for categorical variables. Data on AHI before n-CPAP therapy were compared between the subgroups and were obtained only from subjects who underwent the MWT.

To examine whether objective sleepiness severity (determined by the MWT sleep latency at baseline) would affect the response to modafinil therapy, a comparison of the changes in the ESS total score and mean MWT sleep latency with the treatment was performed between the modafinil and placebo groups using the two-sample *t* test in the two MWT subgroups. Statistical analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC, USA), and statistical significance was set at $p \leq 0.05$.

3. Results

The mean (±standard deviation [SD]) age and BMI of the 50 subjects (47 men and three women) undergoing the MWT were 52.0 ± 10.5 years and 27.3 ± 3.5 kg/m^2, respectively. The mean AHI before and during n-CPAP therapy was 44.1 ± 22.9/h and 3.0 ± 2.7/h, respectively. The mean baseline ESS total score and MWT sleep latency were 14.1 ± 2.8 and 14.2 ± 4.9 min, respectively. The group undergoing the MWT was small but significantly older than that not undergoing the MWT (52.0 ± 10.5 vs 48.1 ± 8.9 years, $p = 0.030$) and included more subjects with cardiovascular complications (42.0% vs 23.4%, $p = 0.043$); no significant differences were observed in regard to sex (male/female, 94.0%/6.0% vs 98.4%/1.6%, $p = 0.317$), BMI (27.3 ± 3.5 vs 27.8 ± 4.1 kg/m^2, $p = 0.508$), AHI during n-CPAP therapy (3.0 ± 2.7 vs 2.5 ± 2.6/h, $p = 0.345$), or ESS score (14.1 ± 2.8 vs 14.7 ± 3.0, $p = 0.291$). There were no statistically significant differences between the two MWT subgroups (MWT sleep latency of <14 min, $n = 23$, and ≥14 min, $n = 27$) in regard to age (52.5 ± 11.0 vs 51.7 ± 10.2 years, $p = 0.787$), BMI (28.1 ± 4.4 vs 26.6 ± 2.5 kg/m^2, $p = 0.147$), cardiovascular complications (47.8% vs 37.0%, $p = 0.567$), AHI before and during n-CPAP therapy (49.5 ± 27.8 vs 39.6 ± 17.0/h, $p = 0.130$; 3.3 ± 3.1 vs 2.7 ± 2.3/h, $p = 0.484$), and ESS score (14.3 ± 2.4 vs 14.0 ± 3.1, $p = 0.742$).

No significant correlation was found between the mean ESS total score and MWT sleep latency at baseline and after treatment with modafinil or placebo ($r = -0.064$, $p = 0.658$ and $r = -0.230$, $p = 0.108$, respectively) (Fig. 1). Changes in the ESS total score and MWT sleep latency after treatment in the two MWT sleep latency subgroups were compared between the modafinil and placebo groups (Table 1). In the <14-min subgroup, the change in the ESS total score after modafinil or placebo treatment was significantly greater in the modafinil group than in the placebo group ($p = 0.005$). In the ≥14-min subgroup, no significant differences in the change of the ESS total score were observed between the two treatment groups ($p = 0.264$). In the <14-min subgroup, the change in MWT sleep latency was significantly greater in the modafinil group than in the placebo group ($p = 0.005$), whereas in the ≥14-min subgroup, no significant difference in sleep latency was observed between the two treatment groups ($p = 0.268$).

4. Discussion

The present study results showed that the mean MWT sleep latency in subjects with residual sleepiness during adequate n-CPAP therapy remained >14 min, which is within the lower normal range defined as two SD from the mean in healthy individuals [15,16]. Previously reported baseline MWT sleep onset latencies of patients with residual sleepiness who underwent modafinil treatment were similar to those in the present study [10]. These findings agree with the International Classification of Sleep Disorders, which states that most OSAS patients with residual sleepiness present with sleep latency of >8 min on the Multiple Sleep Latency Test (MSLT) [17], indicating that the objective sleepiness level is not so high. Thus, the inability to maintain wakefulness, demonstrated by the MWT sleep onset latency level, in subjects with residual sleepiness could be milder than that in cases with primary hypersomnias, including narcolepsy [18,19], and almost in the normal range. Furthermore, there was no correlation between the ESS and the MWT sleep onset latency, suggesting that the subjective sleepiness level is highly divergent from the objective level of the ability to maintain wakefulness. Some patients with residual sleepiness under optimal n-CPAP treatment may overestimate their sleepiness levels. To clarify the mechanism of this phenomenon, analyses of the brain morphology and metabolism and assessment of the psychological status and environmental factors is necessary in a large number of OSAS cases with subjective residual sleepiness.

This study is the first to examine the relationship between baseline MWT sleep latency and the therapeutic effects of modafinil therapy in subjects with residual sleepiness under optimal n-CPAP therapy. Significant differences in the improvement of subjective (ESS total score) and objective (MWT sleep latency) sleepiness were observed between the placebo and modafinil groups in subjects with a mean MWT sleep latency at baseline of <14 min,