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ORIGINAL COMMUNICATION

Udo A. Zifko
Monika Rupp
Sigrid Schwarz
Harald T. Zipko
Eva M. Maida

Modafinil in treatment of fatigue in multiple sclerosis

Results of an open-label study

Abstract *Background* Modafinil is a unique wake-promoting agent that is chemically distinct from traditional stimulants. Results of a placebo-controlled study showed it to improve fatigue in multiple sclerosis (MS) at a dose of 200 mg daily, but not at a dose of 400 mg daily. *Objective* To establish the efficacy, safety and appropriate dose of modafinil in the treatment of fatigue and sleepiness in patients with multiple sclerosis. *Method* A total of 50 patients diagnosed with MS (mean age 40.4 ± 10.3 years, 30 females/20 males; MS type: 36 relapsing remitting, 1 primary progressive, 13 secondary progressive; mean disability level 3.8 ± 1.5 on the Kurtzke EDSS) and complaining of chronic fatigue were enrolled in a prospective 3-month, two-center, open-label study. Efficacy was evaluated with the Fatigue Severity Scale (FSS, score range 0–42), the Epworth Sleepiness Scale (ESS, score range 0–24) and by subjective patient appraisal of change of fatigue, quality of life and overall satisfaction with treatment. Adverse effects (AEs) were recorded throughout the study. Treatment was started with a single daily dose of 100 mg in all patients. In non-responders the dose was increased by 100 mg increments up to a maximum daily dose of 400 mg. *Results* Three patients discontinued modafinil because of AEs (nervousness, dizziness). Two patients (4 %) were treated with 50 mg, 25 (50 %) with 100 mg, 21 (42 %) with 200 mg and 2 (4 %) with 300 mg daily. No patient required 400 mg daily. Mean FSS scores were 30.3 ± 8.5 at baseline and 25.4 ± 3.7 at 3 months ($p < 0.0001$). Mean ESS scores were 9.7 ± 3.9 at baseline and 4.9 ± 2.9 at 3 months ($p < 0.0001$). Self-appraisal of change of fatigue showed clear improvement in 41 patients (87.2 %), some improvement in 4 (8.5 %) and no change in 2 (4.3 %). Overall clinical condition was clearly improved in 43 patients (91.5 %), somewhat improved in 1 patient (2.1 %), and unchanged in 3 patients (6.4 %). No patient reported worsening of overall clinical condition. *Conclusions* Treatment with modafinil significantly improves fatigue and sleepiness and is well tolerated by patients with MS. Unlike the higher dose regimen required in narcolepsy, a low-dose regimen of modafinil is effective in MS.

Key words fatigue · daytime sleepiness · multiple sclerosis · modafinil

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Univ.-Doz. Dr. U. A. Zifko (✉) · M. Rupp, MD · S. Schwarz, MD
Rehabilitationsklinik Pirawarth
Kurhausstr. 100
2222 Bad Pirawarth, Austria
Tel.: +43-25 74/2 91 60
Fax: +43-25 74/2 91 60 60

U. A. Zifko, MD · M. Rupp, MD · S. Schwarz, MD · H. T. Zipko
Arbeitskreis für klinische Forschung in der Neurorehabilitation
Kurhausstr. 100
2222 Bad Pirawarth, Austria

Univ. Prof. E. M. Maida, MD
Department of Neurology
Evangelisches Krankenhaus
Hans-Sachs-Gasse 10–12
1180 Vienna, Austria

Introduction

Fatigue is the most common symptom of multiple sclerosis (MS). Seventy-five to 90 % of patients with MS report having fatigue, and 50 to 60 % describe it as the worst symptom of their disease [10, 11]. Fatigue is significantly associated with reduced quality of life and is also a major reason for unemployment, especially for patients with otherwise minor disability.

The mechanisms underlying abnormal levels of fatigue in MS are poorly understood [12, 23, 26, 32]. Pri-

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mary fatigue is thought to originate in the central nervous system and may have a minor neuromuscular component [35]. Some investigators have shown that fatigue in MS is not associated with brain atrophy or white matter lesions [1, 19, 38]. Direct mechanisms of gray matter involvement contributing to fatigue may include neuronal injury, iron deposition, demyelination, inflammation, or dysfunction of sodium channels in the central or peripheral nervous system [1, 15].

Modafinil is a central alpha-adrenergic agonist with vigilance-promoting properties [31]. It is effective in the treatment of excessive daytime sleepiness in patients with narcolepsy. Modafinil does not cause elation or euphoria and has a limited side-effect profile with only weak peripheral sympathomimetic activity and minimal effects on hemodynamics [9, 8]. The integrity, or architecture, of nighttime sleep is unaffected by modafinil [33]. Its precise mechanism of action is still unknown. Scammel et al. showed selective activation of the tuberomammillary nucleus and orexin neurons of the perifornical areas in the hypothalamus by modafinil in rats [33]. Modafinil does not bind to known adrenergic, gamma-aminobutyric acid (GABA) or serotonin receptors [22]. It increases extracellular dopamine in a hypocretin-receptor 2 – independent manner [40].

In a placebo-controlled study, Rammohan et al. observed a significant improvement of fatigue in MS patients with 200 mg daily, but not with 400 mg daily [29]. Based on an open-label study, Terzoudi et al. reported a positive effect of modafinil, 200 mg daily, on fatigue in MS, which tended to be more pronounced in the early stages of the disease [36].

The objective of this study was to evaluate (1) the tolerability (adverse effects (Aes)), (2) efficacy and (3) optimal dose of modafinil in the treatment of fatigue and daytime sleepiness in patients with multiple sclerosis. A preliminary report has been published elsewhere [42].

Patients and methods

The study was designed as a two-center, 3 month, open-label trial. Modafinil was administered to 50 patients with MS who reported chronic fatigue (30 women, 20 men; mean age of 40.4 ± 10.3 years). Chronic fatigue was defined as a subjective lack of physical and/or mental energy that was perceived by the individual affected or the caregiver to interfere with usual or desired activities for more than 6 weeks [39]. Exclusion criteria included narcolepsy, sleep apnea, use of steroids within the last 3 months, acute exacerbations of MS within the last 8 weeks, prescription or change of dose of antidepressant medication within the last 3 weeks, use of tranquilizers, diabetes mellitus, reduced liver or renal function. MS was diagnosed by the criteria of Poser [28]. The severity of disease was assessed by the Kurtzke Expanded Disability Status Scale (EDSS) [18].

Of the 2 contributing centers, center A was a general hospital with a neurological department specializing in the management of multiple sclerosis. All patients in center A were included and treated on an outpatient basis. Center B was a neurological rehabilitation center. All patients in center B were included in the study during the first week of a 4-week course of in-patient rehabilitation. For all patients, the initial dose of modadinil was 100 mg daily administered as a single dose in the morning. If this failed to improve fatigue, the daily dose of the drug, if well tolerated, was increased to 200 mg and again administered as a single dose. Depending on the response, further 100 mg dose increments up to a maximum of 400 mg daily were made. In all patients the final dose level was reached within 4 weeks.

Daytime sleepiness was evaluated with the German version of the Epworth Sleepiness Scale (ESS) [4]. Daytime fatigue was measured with the Fatigue Severity Scale (FSS) published by Krupp et al. [17]. The occurrence of possible AEs was documented according the protocoll in all patients at the regular follow-up examinations. At the end of the study patients were asked about tolerability (excellent – good – moderate – poor) and efficacy (clear improvement – some improvement – no improvement – deterioration) of the drug. In addition, the overall clinical condition (clear improvement – some improvement – no improvement – deterioration) at the end of the study was compared with that at baseline.

The Statview 4.5 and SPSS 8 software packages were used for descriptive analyses and analyses of signifance (Wilcoxon matched pairs signed rank test).

Results

The mean duration of MS was 6.5 ± 5.3 years. Thirty-six patients suffered from primary relapsing MS, 13 from secondary chronic-progressive MS and 1 from primary chronic-progressive MS. The mean EDSS was 3.8 ± 1.5. Fatigue had been present for a mean of 6.0 ± 5 years.

Three patients dropped out of the study because of adverse effects. Of these, two reported nervousness (40 and 72 days after onset) and one reported an increased severity of pre-existing vertigo (14 days after onset). Tolerability was described as excellent by 43 patients (91.5 %), as good by one patient (2.1 %) and as moderate by three patients (6.4 %). One patient developed an acute episode of MS and was taken off the drug for 5 days.

The mean daily dose of modafinil was 148 ± 61 mg. The median daily dose of modafinil was 100 mg. In 24 patients (51.1 %) a daily dose of 100 mg produced an adequate response, so that upward dose adjustment was unnecessary. Two patients on 100 mg complained of restlessness so that the dose was reduced to 50 mg daily in one patient, and stopped in the other patient. Twenty patients (42.6 %) needed 200 mg daily for an adequate response, while 2 patients (4.3 %) needed 300 mg. No patient received a daily dose of modafinil greater than 300 mg.

Mean FSS scores improved from 30.3 ± 8.5 at baseline to 25.4 ± 3.7 after 3 months of treatment with modafinil (Fig. 1). The difference was significant ($p < 0.0001$). Seventy-eight percent of patients had FSS scores that improved by more than 2 points (Fig. 2). Mean ESS scores also improved significantly from 9.7 ± 3.9 at baseline to 4.9 ± 2.9 after 3 months of treatment with modafinil ($p < 0.0001$). Eighty-nine percent of patients had ESS scores that improved by more than 2 points.

Of the patients who received modafinil treatment for 3 months, 41 patients (87.2 %) reported clear improve-

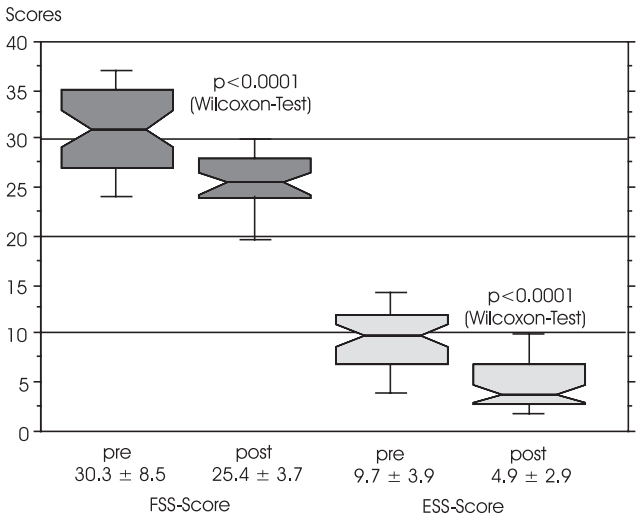

Fig. 1 Note the significant improvement of both FSS and ESS scores.

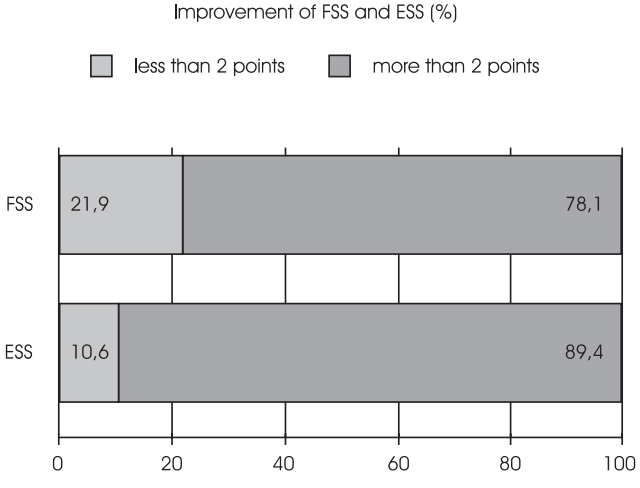

Fig. 2 The figures demonstrates the degree of improvement for the FSS- and ESS-score.

ment, 4 patients (8.5%) reported some improvement and 2 patients reported (4.3%) no improvement of fatigue. No patient reported a deterioration. Overall satisfaction with treatment was good in 43 patients (91.5%), moderate in 1 patient (2.1%) and poor in 3 patients (6.4%).

Response to treatment was not related to patient age, type of MS, EDSS scores, duration of MS, or gender. The dose needed was unrelated to the patient's body weight.

Discussion

The results of this open-label study showed that modafinil (1) is well tolerated by patients with MS, (2) is effective in the treatment of MS-associated fatigue, and (3) can be administered at doses lower than those normally needed in the treatment of narcolepsy.

Modafinil is a central adrenergic agonist, and is effective in the treatment of narcolepsy with and without cataplexy. In most countries this is, in fact, its approved indication. Recently it has, however, been increasingly used for treatment of other conditions such as idiopathic hypersomnia [34], obstructive sleep apnea/hypopnea syndrome [25], Parkinson's disease [13], attention-deficit/hyperactivity disorder [30], and multiple sclerosis [29, 36]. It has also been administered as an adjuvant to antidepressants [20] as well as in the treatment of fatigue and for improving mental performance after sleep deprivation [27].

In patients with MS, fatigue is often responsible for impairments in activities of daily living, unemployment and poor family and social contacts [6]. It also tends to be associated with other symptoms, such as depression [2, 14, 16] or sexual dysfunction [43]. To date, drug treatment has been only partially successful in alleviating fatigue, and effects vary widely from patient to patient [5, 6]. The low side effect profile of modafinil, its successful use in narcolepsy, the positive results of two preliminary studies on MS-associated fatigue [29, 36] and anecdotal patient reports [41] prompted us to evaluate the clinical efficacy and, specifically, the dose needed in a larger group of MS patients complaining of chronic fatigue. Modafinil, 400 mg, was reported to be superior to lower doses in the treatment of narcolepsy [3, 37]. By contrast, in patients with MS-associated fatigue, Rammohan et al. found daily doses of 200 mg of modafinil to be effective, while 400 mg doses were not. As a result, the patients in our study were started on 100 mg daily with dose increments for non-responders, if needed. The lower doses, i. e. 100 and 200 mg daily, proved to be effective in more than 90% of patients. Two patients even did well on no more than 50 mg.

Although the causes underlying narcolepsy are not fully understood, reduced hypocretin secretion was found to be a factor both in animal studies and in humans [24]. Narcolepsy is known to be associated with HLA-DR2 and DQB1*0602 [22], and shows similarities with MS at least in terms of HLA association. However, the mechanisms underlying fatigue in MS are not yet fully understood. But there is evidence suggesting that additional mechanisms, particularly an involvement of cortical pathways rostral to the pyramidal tract [32] and peripheral abnormalities, contribute to fatigue [22, 23]. The differences in the mechanisms leading to narcolepsy and MS may well be responsible for the differences in the doses required to effectively treat the two conditions.

The treatment with modafinil in patients with MS showed excellent tolerability in this study. Only three patients stopped treatment with modafinil because of the

occurrence of possible side effects, such as restlessness, nervousness and aggravation of pre-existent vertigo. All three patients suffered from these symptoms after onset of modafinil at a dose of 100 mg. In two patients the nervousness they had experienced at a dose of 100 mg improved on 50 mg without any loss of effect on fatigue. Other adverse effects were absent throughout, but it should be remembered that patients with pre-existent kidney or liver disease were not eligible for the study. Modafinil thus appears to be very well tolerated by patients with MS and is usually effective at relatively low doses.

The interpretation of the results obtained in the present study is admittedly limited by the open-label non-placebo-controlled design of the study, by the use of unidimensional scores to assess efficacy and by the omission of objective sleep studies. But the outcome is, no doubt, a positive signal which should encourage further trials with a double-blind design, particularly as the drug is very well tolerated by MS patients. The absence of a correlation with the duration, severity and type of MS, as well as with patient age, body weight or gender, underscores the usefulness of modafinil in these patients and makes it a novel candidate treatment option for use in treating fatigue, the most common symptom of MS.

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Addendum After the acceptance of this manuscript the study from Rammohan et al. was published as full article:

Rammohan KW, Rosenberg JH, Lynn DJ, Blumenfeld AM, Pollak CP, Nagaraja HN (2002) Efficacy and safety of modafinil (Provigil®) for the treatment of fatigue in multiple sclerosis: a two centre phase 2 study. J Neurol Neurosurg Psychiatry 72: 179–183

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