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Preliminary Observations Suggesting That Treatment With Modafinil Improves Fatigue in Patients With Orthostatic Intolerance

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Many patients who suffer from orthostatic intolerance (OI) may also have severe fatigue and extreme exercise intolerance. In some of these patients, fatigue may be so severe that they are unable to maintain employment. In some, even the activities of the daily living may be compromised. We report on the use of modafinil in a subgroup of patients who failed therapy with commonly used medication for fatigue in patients with OI. The study was approved by the institutional review board. A retrospective nonrandomized analysis was preformed on 60 patients evaluated at our autonomic center for OI from 2003 to 2010. The diagnosis of OI was based on patient history, physical examination, and reponse to head up tilt table testing. All these patients had fatigue as their predominant symptom. Multiple trials of stimulants including methylphenidate, amphetamine, or dextroamphetamine failed to provide symptomatic relief of fatigue in these patients. Each patient received modafinil (100–200 mg daily). The mean follow-up period was 9 ± 3 months. A treatment was considered successful if it provided symptomatic relief from fatigue for the patient. Sixty patients, age 29 ± 15, 52 women were included in the analysis. Migraine (57%) and joint hypermobility syndrome (33%) were common comorbidities. Out of 60 patients, 40 patients reported initial improvement with initiation of modafinil therapy. Twenty patients reported no change in their symptoms of fatigue. Of the 40 patients who showed initial improvement in their symptoms 4 had eventual recurrence of fatigue after 3 months of modafinil therapy. Thirty-six patients continued to demonstrate symptom relief from fatigue for more than 6 months. In a selective group of patients of OI, modafinil may improve fatigue.

Keywords: modafinil, postural orthostatic tachycardia, orthostatic intolerance, fatigue

INTRODUCTION

Orthostatic intolerance (OI) refers to a heterogeneous group of disorders of hemodynamic regulation characterized by insufficient cerebral perfusion resulting in symptoms upon standing and relieved by becoming supine. Symptoms may include syncope, near syncope, lightheadedness, exercise intolerance, palpations, cognitive impairment, headache, and fatigue. OI reflects an inability of the autonomic nervous system to adequately respond to the orthostatic stress of gravity. The autonomic disorders resulting in orthostatic intolerance can be divided into these broad groups: reflex syncope, postural tachycardia syndrome, and autonomic failure. The details of these conditions and their diagnosis are reviewed in detail elsewhere.[1–3] Many patients who suffer from OI may also have severe fatigue and extreme exercise intolerance. In some of these patients, fatigue may be so severe that they are unable to maintain employment. In some, even the

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activities of the daily living may be compromised. Various pharmacologic agents including, methylphenidate, amphetamine, and dextroamphetamine have been used for the treatment of fatigue in this patient population (although there are no randomized placebo controlled trials to support use of this approach).[3–5] We report on the use of modafinil in a subgroup of patients who failed therapy with commonly used medication for fatigue in patients with OI. Modafinil has been used with variable success for the treatment of fatigue in patients with multiple sclerosis,[6–9] Parkinsonism,[10,11] and schizophrenia.[12] In addition, modafinil has been used for the treatment of fatigue associated with cancer, motor neuron disease, and depression.[13–15]

METHODS

A retrospective nonrandomized analysis was preformed on 60 patients evaluated at our autonomic center for OI from 2003 to 2010. The study was approved by the institutional review board. OI refers to a heterogeneous group of disorders of hemodynamic regulation characterized by insufficient cerebral perfusion resulting in symptoms during upright posture relieved by recumbency. Symptoms included syncope, near syncope, fatigue, palpitations, exercise intolerance, lightheadedness, diminished concentration, and headache. In a retrospective chart review, we collected data including demographic information, presenting symptoms, laboratory data, tilt-table response, and treatment outcomes. The protocol used for tilt table testing has been described elsewhere, but basically consisted of a 70-degree baseline upright tilt for a period of 30 minutes, during which time heart rate and blood pressure were monitored continually. If symptomatic hypotension and bradycardia occurred, reproducing the patient's symptoms, the test was ended. If no symptoms occurred, the patient was lowered to the supine position and an intravenous infusion of isoproterenol started with a dose sufficient to raise the heart rate to 20%–25% above the resting value. Upright tilt was then repeated for a period of 15 minutes. These data were categorized into 3 groups based on the positive tilt-table pattern: neurocardiogenic, dysautonomic, and postural orthostatic tachycardia syndrome (POTS). The treatment protocols employed were based on our previous experiences with orthostatic disorders and are described in detail elsewhere.[1–5] We identified 60 patients of OI with fatigue refractory to other commonly employed medication. Briefly, a sequence of therapies was employed that included physical counter maneuvers and increased dietary fluids and sodium. If these were ineffective, pharmacotherapy was initiated in a sequence generally consisting of fludrocortisone, midodrine, methylphenidate, selective serotonin reuptake inhibitors, pyridostigmine, and erythropoietin either alone or in combination. A trial of stimulants including methylphenidate, amphetamine or dextroamphetamine failed to provide symptomatic relief of fatigue in these patients. All of these patients were subsequently tried on modafinil (between 100 and 200 mg daily). We did not employ a formal questionnaire to assess the response to treatment nor did we assess the response to treatment with head up tilt table testing (HUTT) testing. The information about the subjective symptoms and sense of well being from each patient were collected from the patient charts, physician communications, and direct patient inquiry. A treatment was considered successful if the patient that it provided symptomatic relief from fatigue.

These patients were diagnosed as having OI primarily based on their history, clinical features, and findings from head upright tilt table testing. They were diagnosed to suffer from POTS if they had symptoms (>6 months) of orthostatic intolerance associated with a heart rate increase of 30 bpm (or rate that exceeds 120 bpm) that occured within the first 10 minutes of standing or upright tilt, and was not associated with other chronic debilitating conditions such as prolonged bed rest or the use of medications known to diminish vascular or autonomic tone.

RESULTS

Eighty-five patients, aged 30 ± 15, 74 of whom were women with OI and refractory fatigue, were initially identified for inclusion in this retrospective analysis. One patient had incomplete follow-up (<6 months), one had developed intolerance (increased anxiety and jitteriness), and 23 patients were unable to obtain the medication. These 25 patients were excluded from the analysis. Sixty patients, aged 29 ± 15, 52 of whom were women, were finally included in the analysis.

Table 1 summarizes the clinical feature, comorbid conditions, precipitating events, and symptoms of OI in these 60 patients.

Migraine (57%) and joint hypermobility syndrome (33%) were common comorbidities in these group of patients. All of these patients had fatigue as a predominant symptom.

Response on HUTT: All patients had HUTT and all had had a positive tilt table study that reproduced their clinical symptoms. Among those having an abnormal tilt table pattern, 41(68%) had a postural orthostatic tachycardia response, 10 (17%) had a neurocardiogenic response, and 9 (15%) had a dysautonomic response.

Table 1. Clinical features of patients with POTS and drug refractory fatigue.

Total number of patients screened	85
No. of patients included in analysis	60
No. of patients with incomplete follow-up	1
No. of patients with intolerance to study drug	1
No. of patients who could not receive the study drug	23
Clinical features in patients included for analysis	
Age(yrs)	29 ± 15
Females (N, %)	52 (87%)
Comorbidities (N, %)	
Joint hypermobility	20 (33%)
Hypertension	10 (17%)
Diabetes mellitus	4 (6%)
Migraine	34 (57%)
Precipitating event	
Infectious mononucleosis	2
Pregnancy	2
Surgery	1
Trauma	1
Clinical symptoms of POTS	
Fatigue	60 (100)
Presyncope	42 (70)
Syncope	30 (50%)
Inability to concentrate	21 (35%)
Orthostatic palpitations	35 (58%)

All these patients had failed various combinations of therapies (midodrine, methylphenidate, amphetamine, and dexamphetamine) directed at relieving their fatigue. The mean follow-up period has been 9 ± 3 months. Each patient recieved modafinil (100–200 mg) subsequently.

Response to therapy

Out of 60 patients, 40 patients reported initial improvement with initiation of modafinil therapy. Twenty patients reported no change in their symptoms of fatigue. Of the 40 patients who showed initial improvement in their symptoms 4 had eventual recurrence of fatigue after 3 months of modafinil therapy. Thirty-six patients continued to demonstrate symptom relief from fatigue for more than 6 months.

Daily activities and lifestyle

Each of the patients reported a constant fatigue precipitated by ordinary day to day activities. Their feeling of being fatigued all the time had greatly limited their daily activities to a point that they suffered such anxiety at the thought of minimal activity that they became effectively homebound.

DISCUSSION

Modafinil was approved by U.S. FDA for the treatment of excessive day time sleepiness in patients with obstructive sleep apnea. In addition, it has been reported to improve cognitive function, psychomotor retardation, and mood problems with narcolepsy. In patients with obstructive sleep apnea it also improves symptoms of depression, anxiety, and irritability.[16]

The pharmacologic effects of modafinil are complex and it is thought to alter various neurotransmitters in the brain.[17] In animal studies, modafinil has been reported to decrease the levels of inhibitory neurotransmitters gamma amino butyric acid and increase the levels of glutamate and serotonin.[18–20]

Modafinil has been reported to improve fatigue in patients with multiple sclerosis,[7–9] Parkinsonism,[10,11] and patients treated with cancer chemotherapy for various malignancies.[13–15]

Our study populations' predominant complaint was of fatigue and various trials of medications with multiple stimulants either alone or in combination had failed to relieve their symptoms. The modest response seen in this patient population which was refractory to other medication is encouraging. By improving fatigue in our patient population, many of our patients could resume their activities of daily living without much limitation. An important yet neglected consequence of these disorders is the tremendous social and emotional toll that these diseases take on both patients and their families. In addition, both patients and their treating physicians should be aware of the fact that these disorders tend to be chronic and that the treatment is only palliative and not curative. Although, the use of modafinil was not randomly allocated, and there was no control group for comparison in this analysis we still feel that these preliminary observations with the use of madafinil will hopefully lay a foundation for a prospective randomized placebo controlled trial in patients suffering from OI.

LIMITATIONS

There are several important limitations to our study. The study group itself was small, and it was not a randomized controlled trial. Rather, each patient was used as their own control. In addition, patients with OI may exhibit spontaneous variations in symptom severity. Hence, we cannot be absolutely sure that the beneficial effects noted can be wholly attributed to the actions of the drug. However, this group of patients was highly symptomatic with dominant symptom of fatigue who had not responded to any other

therapeutic modality. Thus, it seems reasonable to conclude that madafinil contributed to the beneficial effects noted. Finally, the patients presented here all tended to have unusually severe forms of the disorder, and therefore may not be representative of the majority of patients with OI.

CONCLUSIONS

In a selective group of patients who suffer from OI, modafinil may improve fatigue. Prospective randomized double-blinded controlled study may help answer many of the unresolved issues this study could not address.

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