Sleep Science 7 (2014) 65–68

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Case Report

Experience with the use of modafinil in the treatment of narcolepsy in a outpatient facility specialized in diurnal excessive sleepiness in São Paulo ☆

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ARTICLE INFO

Article history:
Received 24 July 2013
Accepted 10 March 2014
Available online 20 August 2014

Keywords:
Modafinil
Narcolepsy
Treatment
Diurnal excessive sleepiness

ABSTRACT

Narcolepsy is a chronic neurological disease characterized by diurnal excessive sleepiness and catapleaxy. It affects 1 in every 2000 to 4000 individuals with personal, social and familiar significant repercussions. The treatment of narcolepsy is mainly based on the use of stimulants for the control of the diurnal excessive sleepiness, in conjunction with behavioral measures and sleep hygiene. Among the stimulants, modafinil has presently been the drug of choice for the treatment of the diurnal excessive sleepiness in patients with narcolepsy. In the worldwide experience, its use is better tolerated and the majority of its side effects is considered light or moderate. However, the clinical use in Brazil was initiated at the end of 2008, with little experience on the narcolepsy population of this country. In this context, the objective of this study was the evaluation of the use of modafinil, verifying the indication of use, causes for discontinuation, daily dosage, efficiency of the treatment in a patient sample of narcoleptics consulted in a specialized center in Brazil. In this study, modafinil was effective for the control of the symptoms related do narcolepsy in 66% of the studied patients. The side effects such as headache, parestesias and diarrhea were the main reasons for the discontinuation of treatment with modafinil. It is important to clinically follow up the patients for a long period to evaluate symptomatology, control of use, tolerability and re-evaluation of the more effective therapeutic dosage able to control narcolepsy. Due to its high cost and clinical benefits, this drug should be on the government's list of free drugs for the treatment of these patients.

☆Support: AFIP & FAPESP – CEPID 98/14303-3.
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Peer review under responsibility of Brazilian Association of Sleep

http://dx.doi.org/10.1016/j.slsci.2014.07.017

1. Introduction

Narcolepsy is a chronic neurological disease characterized by diurnal excessive sleepiness (DES), sleep paralysis, hypnagogic or hypnopompic hallucinations and cataplexy [1]. Narcolepsy with cataplexy represents about 60–70% of all attended cases in treatment centers for these patients [2,3]. Actually, we know that narcolepsy with cataplexy and the deficiency of hypocretin are associated with polymorphism of the human leukocyte antigen HLA-DQB1*0602, altered levels of CD40L and *T* cell receptors, suggesting that an autoimmune process might be involved [3].

Narcolepsy affects 1 in every 2000–4000 individuals in the general population and the treatment aims to control the diurnal excessive sleepiness (DES), nocturnal complaints of sleep fragmentation, cataplexy and psychosocial adaptation [4,5]. DES is treated with sleep hygiene measures, programmed naps and social measures (working time adaptation to accommodate for naps). Stimulant medications are also utilized to increase awareness, such as modafinil and methylfenidate [2]. For the control of cataplexy, tricyclic antidepressants can be used, serotonin-reuptake inhibitor antidepressants and dual antidepressants, besides some other drugs such as sodium hydroxybutyrate (not available in Brazil) [4].

Modafinil is a non-amphetamine stimulant that promotes the vigil state, whose mechanism of action is still not fully understood. However, it has been demonstrated that modafinil acts via the blockage of dopamine transporter (DAT) and also the noradrenalin transporter (NET). Besides having these adrenergic effects, modafinil also acts as agonist of the hypocretin-1 system, something not detected among the traditional stimulants. Modafinil has been utilized as the treatment of choice for DES because it acts over more specific brain areas such as the anterior and lateral region of the hypothalamus and for demonstrating much less side effects, such as addiction and cardiovascular disorders [4,6].

Its clinical use was initiated more consistently in Brazil at the end of 2008, after the approval of its normal commercialization by the National Sanitary Vigilance Agency (ANVISA). For this reason, there is very little experience of the use of modafinil for the control of narcolepsy in the population with narcolepsy in Brazil. In this sense and considering the need for a larger view of the use of modafinil in the abovementioned population, the objective of this study was the evaluation of modafinil in the treatment of diurnal excessive sleepiness in a population of patients with narcolepsy attended by a Sleep Center in the country.

2. Methods

This study is a retrospective study and was approved by the Ethical Committee of Research of the Federal University of São Paulo (1802/07). Hundred and twenty two patient files of patients with diagnosis of narcolepsy with regular follow up by the outpatient facility of Diurnal Excessive Sleepiness of the Federal University of São Paulo were analyzed. The clinical and electrophysiological criteria for the diagnosis of narcolepsy follow the American Academy of Sleep Medicine's criteria [1]. Inclusion criteria were patients with narcolepsy with regular follow up by the unit and with files that had complete and legible information. Exclusion criteria included patients already medicated with modafinil before the first consultation, with history of allergy to the drug or that had no financial condition to buy the medication.

Modafinil was first prescribed at the Outpatient Facility of Excessive Sleepiness for the narcolepsy patients in 20/03/2008. The inicital standard dose was 100 mg per day, with progressive increase of 100 mg every return, under clinical scrutiny. The criterion parameter used for the control of DES was subjective and it was for the improvement of the Epworth Sleepiness Scale (ESS) scores. However, the files did not contained all noted information referring to the ESS scores for every return, which did not make it possible for the clinical team to use them as parameters.

3. Results

Of the 122 patients, 11 patients (9,1%) utilized modafinil as a single drug, 60 (49,2%) patients were treated with methylfenidate and 51 patients (41,7%) used modafinil in association with other drugs such as Ritalin, tricyclic antidepressants, serotonin-reuptake inhibitors, anticonvulsants, serotonin and noradrenalin-reuptake inhibitors (Table 1).

Among the main reasons for discontinuation of modafinil in 25 patients, we can mention the side effects and poor clinical improvement (Table 2). Among the side effects, the major one was headache, comprising about 1/3 of the patients using modafinil (Table 3).

The most prescribed modafinil dose for the control of DES was 200 mg daily. This dose was used in 45.3% of the cases of narcolepsy treated with modafinil. However, in 4 cases, there was the need to increase the dosage above 200 mg for the control of the clinical symptoms.

4. Discussion

In worldly experience, the use of modafinil is reported as being well tolerated by the patients with narcolepsy and the majority of side effects is considered light or moderate [6]. This study demonstrates the use and safety of this drug for the treatment of DES in our population of narcoleptics. However, the difficulties to access the medication due to its high cost and the lack of public availability through our national health system creates severe barriers for its regular use for the majority of our population.

Among the side effects, the most common was headache (10–26%), followed by nervousness or anxiety, nausea, dry mouth, diarrhea, asthenia and insomnia [6,7]. These side effects were resolved with the discontinuation of modafinil, confirming our findings and showing that the side effects prevail as limiting factors for the continuity of treatment with modafinil [6–8]. However, the financial limitation of several patients was, and continue being, a very important and limiting factor for the continuity of the treatment [8–10].

We know that the cost of modafinil therapy is very superior of the one with methyphenidate. The treatment

Table 1 – Pharmacological treatment of patients with the diagnosis of narcolepsy.

Last pharmacological treatment in the patient's file	Narcolepsy with cataplexy		Narcolepsy without cataplexy		Total	%	% per group of treatment
	♀	♂	♀	♂			
	34	39	27	22	122	100	
Modafinil	2		4	5	11	9.01	9.01
Modafinil+Ritalin		2	2		4	3.28	
Modafinil+Ritalin+Tricyclic	1	1			2	1.64	
Modafinil+Ritalin+IRSS[a]	1	3		2	6	4.92	
Modafinil+Ritalin+IRSS+Anticonvulsant	1				1	0.82	
Modafinil+Tricyclic	1				1	0.82	
Modafinil+Anticonvulsant		1			1	0.82	
Modafinil+Ritalin+Tricyclic+IRSS		1			1	0.82	
Modafinil+Ritalin+IRSS+SNRIs[b]			1		1	0.82	19.38
Other medications but not modafinil	22	24	13	12	71	58.20	58.20
No prescribed medication	5	5	4	2	16	13.11	13.11
Total	34	39	27	22	122	100	100

[a] Serotonin-reuptake inhibitor.
[b] Serotonin and noradrenalin-reuptake inhibitor.

Table 2 – Motives for discontinuation of the use of modafinil (some of them are over layered in the same patient).

	Number of cases	Frequency (%)
Side effects	9	36
Poor clinical improvement	5	20
No specified motive	5	20
High cost	4	16
Pregnancy	1	4
Bariatric surgery pre op	1	4
Total	25	100

Table 3 – Frequency of side effects on several patients.

	Patients
Headache	3
Diarrhea, nausea and leg pain	1
Tingling in legs	1
Sleepiness, increase in hallucinations and acne	1
Important memory loss	1
Abortion	1
Non specified discomfort	1

option with methylphenidate in relation with modafinil must be taken based on clinical criteria, the safety of the treatment with sympathomimetic drugs, or the associated risks for every patient. In parallel, the association of drugs for the control of cataplexy must be evaluated in these cases [7–10].

In any case and independently of the pharmacological treatment of choice, there must be a regular patient follow up to verify the side effects, including sleep disturbances, humor changes, methabolic and cardiovascular abnormalities. This way, this follow up is also important to determine treatment adherence and treatment response, monitor drug safety and be prepared to solve any social or occupational hazard that might appear during the course of treatment, when the symptoms of narcolepsy are not well controlled [8–10].

The choice for the treatment with modafinil must be done after a precise indication for the control of DES. Even though with the significant improvements on the understanding of narcolepsy's physiopathology, there is still no treatment that completely recovers and maintains awareness during the entire day [7,8]. In this context, initial and progressive doses and constant monitoring are essential, even though, modafinil is the drug with the safest profile compared to others. The regular follow up of the patient facilitates the identification of early complications with the discontinuation of modafinil, if necessary and the evaluation of the clinical response seems to be the correct way to manage the therapy.

5. Conclusions

(1) This study demonstrates the safety of the use of modafinil for the treatment of DES in patients with narcolepsy attended by our specialized center.
(2) Side effects as headache, anxiety, nausea, dry mouth, diarrhea, asthenia and insomnia are reversible after discontinuation of the drug.
(3) The medication should have been included in the list of free medications available to the general public due to its high cost and good results for these patients.

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