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Modafinil: A Double-Blind Multicentric Study

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Summary: Modafinil is a central putative alpha-1 postsynaptic agonist with vigilance-promoting properties. Fifty narcoleptics (33 male and 17 female) participated in a multicentric study aimed at assessing the effects of the compound on night sleep, feeling on awakening, excessive daytime sleepiness and cataplexy. Modafinil was administered in a double-blind cross-over design at a daily dosage of 300 mg versus placebo. The duration of the study was 12 weeks, including a 2-week "run in" period with placebo, a first 4-week treatment period with either modafinil or placebo, a 2-week wash-out period with placebo and a second 4-week treatment period with either placebo or modafinil. Daily evaluation was based on a sleep log, visual analog scales, a sleep questionnaire and a clinical global index. Sleep laboratory evaluation took place on nights 1, 28, 42 and 70. It included 1 night of polysomnography preceded by a questionnaire on therapeutic and side effects, and a maintenance of wakefulness test (MWT). Sleep logs did not show any modification of night sleep, but a reduction of daytime sleepiness and sleep. Feeling on awakening was not modified. An overall benefit was noted by physicians as well as by patients. MWT disclosed a positive effect of modafinil on excessive daytime sleepiness. Cataplexy was not modified. **Key Words:** Modafinil—Alpha adrenergic agonist—Maintenance of wakefulness testing—Sleepiness—Cataplexy.

Modafinil, a putative alpha-1 postsynaptic agonist, is a new compound with alerting properties. Locomotor activity is enhanced in both the rat (1) and the monkey (2). This effect is blocked by previous administration of prazosine, an alpha-1 adrenergic receptor blocker. In humans the kinetics of the compound is linear for doses from 50 to 400 mg. Plasma peak shows up 2–3 hours after oral ingestion, and the elimination half-life is 8–10 hours. Up until now it has been investigated in open studies showing good or very good results in 60–70% of the subjects (3–6) and in a single double-blind study (7). The aim of the present study was to further investigate the effects of the compound on the symptoms of narcolepsy.

SUBJECTS AND METHODS

Fifty narcoleptic subjects (33 male and 17 female) 40.88 ± 13.27 years of age, were selected in four different centers (Montpellier, Montreal, Paris and Créteil) according to the same criteria, e.g. excessive daytime sleepiness and cataplexy, a mean sleep latency of less than 7 minutes and two or more sleep onset rapid eye movement episodes on the multiple sleep latency test (MSLT), and an association with HLA DR2-DQ1. Mean duration of the condition was 14.51 ± 13.98 years. Subjects were either free of drugs or had discontinued any psychostimulant mediation for at least 14 days before entering the study. Anticataplectic drugs were continued in a few subjects with severe cataplexy, at a maximum daily dosage of clorimipramine 50 mg or fluoxetine 20 mg.

Modafinil was administered in a double-blind cross-over design, at a dosage of 300 mg with either 100 mg in the morning and 200 mg at noon, or 200 mg in the morning and 100 mg at noon, versus placebo. The duration of the study was 12 weeks, including a 2-week "run in" period during which subjects received placebo, a first 4-week treatment period with either modafinil or placebo, a 2-week wash-out period with placebo and a second 4-week treatment period with either placebo or modafinil. At the beginning and at the end of each treatment period subjects spent 24 hours in the sleep laboratory.

Throughout the study subjects filled out a sleep log at home (nighttime total sleep time, number of awakenings, wake time after sleep onset, daytime total sleep time, number of episodes of sleepiness and number of

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TABLE 1. *Nighttime sleep, daytime sleep and cataplexy (sleep log)*

	Placebo	Modafinil	Sequence factor		Drug factor	
			F	p	*F*	p
Nighttime						
Total sleep time (hours) (n = 46)	8.03 ± 1.20	7.94 ± 0.90	0.60	0.44	0.68	0.29
Wake time after sleep onset (hours) (n = 45)	1.20 ± 4.58	0.50 ± 0.71	1.01	0.32	1.12	0.29
No. of awakenings (n = 45)	0.72 ± 0.98	0.65 ± 0.93	0.81	0.37	1.41	0.24
Daytime						
No. of episodes of sleepiness (n = 46)	1.30 ± 1.41	0.95 ± 0.82	0.19	0.67	4.08	0.05
Total sleep time (hours) (n = 46)	0.78 ± 0.78	0.53 ± 0.51	0.08	0.78	16.22	0.0002
Cataplexy (no.) (n = 46)	0.32 ± 0.70	0.22 ± 0.47	0.92	0.34	1.80	0.19

cataplectic attacks), visual analog scales (sleepy, irritable, tired, fit), a sleep questionnaire (sleep latency, easiness to fall asleep, depth of sleep, recuperative value of sleep, number of night awakenings, total sleep time, feeling tired, somnolent and tense on awakening) and a clinical global index (CGI).

Sleep laboratory evaluation took place on nights 1, 28, 42 and 70. It included 1 night of polysomnography (2230–0730 hours), which was preceeded by a questionnaire on therapeutic effects and side effects, judged both by a physician blind with regard to the nature of the treatment and by the patient, and was followed by maintenance of wakefulness testing (MWT) performed at 1000, 1200, 1400, 1600 and 1800 hours, with the subject seated in a comfortable armchair and the lights turned out. In addition, physical parameters (supine blood pressure, maximum and minimum, standing blood pressure, maximum and minimum, supine and standing heart rate) were recorded.

Basal homogeneity of the two sequences (before administration of either placebo or modafinil) was tested with a one-way analysis of variance (ANOVA). Objective and subjective parameters were tested with a multifactor ANOVA for repeated measures, including a period factor (before/after), a drug factor (placebo vs. modafinil), a time factor (when several measures were performed during the daytime) and an interaction between period factor and drug factor. All data were analyzed using SAS procedures (6.07 version).

RESULTS

Nighttime sleep, daytime sleep and cataplexy (sleep log). There was no variation in the night total sleep time, in the duration of wake time after sleep onset or in the number of night awakenings. On the other hand, there was a significant reduction in the number of episodes of sleepiness (p = 0.05) and in the duration of daytime total sleep time (p = 0.0002). Number of cataplectic attacks did not vary (Table 1).

Feeling on awakening (visual analog scales). Visual analog scales did not show any modification of the following items: sleepiness, irritability, tiredness and fitness (Table 2).

Sleep continuity and quality (sleep questionnaire). Sleep questionnaires did not disclose any significant modification of sleep continuity or quality (Table 3).

Clinical global index (CGI). Results were higher with modafinil (2.29 ± 1.06) than with placebo (2.00 ± 0.98); however, this difference did not reach significance (Table 4).

Therapeutic effects. Therapeutic effects were judged by both physicians and patients. An overall clinical benefit was noted by physicians (p = 0.01) and by patients (p = 0.005) (Table 5).

As could be expected there were good and poor responders. Subjects were considered as good responders when the score obtained on modafinil was greater than the score obtained on placebo + 10. According to this

TABLE 2. *Feeling on awakening (visual analog scales)*

	Placebo	Modafinil	Drug factor	
			F	p
Sleepy (n = 44)	42.43 ± 30.44	34.07 ± 26.91	0.63	0.43
Irritable (n = 43)	19.51 ± 21.54	23.63 ± 25.51	1.57	0.22
Tired (n = 45)	42.04 ± 26.23	41.98 ± 28.90	0.72	0.40
Fit (n = 43)	55.95 ± 27.76	52.16 ± 26.00	0.03	0.87

Results are expressed in millimeters.

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TABLE 3. *Sleep continuity and quality (sleep questionnaire)*

	Placebo	Modafinil	Drug factor	
			F	p
Sleep latency (minutes) (n = 45)	14.18 ± 27.37	17.82 ± 37.06	1.96	0.17
Easiness to fall asleep (n = 45)	28.44 ± 31.80	25.82 ± 33.34	0.04	0.84
Depth of sleep (n = 43)	49.44 ± 31.92	44.33 ± 31.42	0.30	0.58
Recuperative value of sleep (n = 40)	45.10 ± 27.83	42.25 ± 29.18	1.25	0.27
No. of night awakenings (n = 40)	3.90 ± 3.70	3.70 ± 4.63	0.65	0.43
Total sleep time (hours) (n = 40)	7.03 ± 1.49	6.91 ± 1.76	0.04	0.84

criterion the percentage of good responders judged by physicians was 56.8%. Table 6 shows that the distribution of good and poor responders varied according to the sequence. There were more good responders in the sequence placebo–modafinil (63.99%) than in the sequence modafinil–placebo (35.99%) ($\chi^2 = 6.15$, p = 0.01). According to the above-defined criterion, the percentage of good responders judged by the patients was 54.35%. Likewise, there were more good responders in the sequence placebo–modafinil (60%) than in the sequence modafinil–placebo (40%); however, the difference did not reach significance ($\chi^2 = 3.25$, p = 0.07).

Side effects. There were significantly fewer side effects on modafinil than on placebo, as judged by both physicians (p = 0.006) and patients (p = 0.0004) (Table 7).

Excessive daytime sleepiness (MWT). Basal values before administration of either of the two compounds (placebo and modafinil) were statistically homogeneous [$F(1.41) = 0.35$, p = 0.56]. There was no sequence effect [$F(1.41) = 1.57$, p = 0.22]. There was a significant improvement in the results of the MWT for patients on modafinil in comparison with placebo (Fig. 1). This included a period effect [$F(1.42) = 3.25$, p = 0.08], a time effect with the highest value (least somnolent) at 1200 hours and the lowest value (most somnolent) at 1600 hours [$F(4.39) = 3.79$, p = 0.01], and a significant interaction effect (drug/period) [$F(1.42) = 14.70$, p = 0.0004], indicating a positive effect of modafinil on excessive daytime sleepiness.

In addition, we looked at the results of the MWT in the good responders only (n = 23). Again there was a significant improvement in the results of the MWT for patients on modafinil in comparison with placebo (Fig. 1). There was no period effect [$F(1,22) = 2.64$, p = 0.12] and no time effect [$F(4,19) = 1.87$, p = 0.16], but there was a significant interaction effect (drug/period) [$F(1,22) = 6.93$, p = 0.02]. However, the difference between the improvement of the results in the good responders only (2.81) and the improvement of the results in the total sample (2.49) was not important.

Peripheral effects. Neither blood pressure nor heart rate varied significantly after either placebo or modafinil (Table 8).

DISCUSSION

As already mentioned, this study was preceded by a single double-blind cross-over study (7), which showed a significant decrease of both diurnal yawnings and irresistible episodes of sleep. Night total sleep time was not modified. However, this study used self-evaluation diaries as the only mode of evaluation. In the present study we used both subjective (sleep log, visual analog scales, sleep questionnaires, judgment on therapeutic and side effects by both physicians and patients, clinical global index) and objective (MWT) modes of evaluation. The choice of the MWT rather than the MSLT followed Mitler's experience that the MSLT is less sensitive than the MWT to treatment-related changes (8). Moreover, it has been our clinical experience with this drug that narcoleptics in a recumbent position may very well fall asleep even while on medication.

In spite of the arbitrary mode of selection of good

TABLE 4. *Clinical global index*

	Placebo	Modafinil	Drug factor	
			F	p
Clinical global index (n = 45)	2.00 ± 0.98	2.29 ± 1.06	1.76	0.19

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TABLE 5. *Therapeutic effects judged by physicians and patients*

	Placebo	Modafinil	Drug factor	
			F	p
Physicians (n = 44)	38.32 ± 34.26	57.09 ± 31.20	7.00	0.01
Patients (n = 46)	37.54 ± 34.58	57.72 ± 29.87	8.81	0.005

and poor responders, the results obtained allow some remarks. Modafinil, as other drugs used to treat excessive daytime sleepiness, does not bring positive results in all patients. Parkes (9) indicated that approximately one third of all narcoleptics have a good and sustained response to dextroamphetamine 10–30 mg daily, one third a satisfactory response and another third little benefit. Among eight patients recruited in a methamphetamine study (10), at least two subjects did not show great improvement on the MSLT.

As for the sequence effect in good responders versus poor responders, this does not come as a surprise. Considering the length of the study (12 weeks), subjects were particularly anxious to perceive an effect of the drug when it was given during the second 4-week treatment period. Conversely, subjects receiving the drug during the first 4-week treatment may still expect to perceive better effects during the second 4-week treatment period. In addition to the results shown by the whole sample on the MWT, we looked at the results shown by the good responders only. The difference between the improvement in the results from the good responders only and the improvement in the results from the whole sample (0.32) was not striking. This might be due in part to the rather severe condition of the MWT testing, in which the subject is in the dark.

An interesting result of this study was the modification of the profile of sleep latencies on the MWT throughout the day from placebo to modafinil. Indeed narcoleptics showed a flat profile of MWT latencies while on placebo and a normalized profile with longer sleep latencies in the morning (1000 and 1200 hours) and in the late afternoon (1800 hours) and shorter sleep latencies at 1400 and 1600 hours. This modification on modafinil was even more manifest in good responders than in the total sample of subjects. This confirms that not only does modafinil induce a better level of

TABLE 6. *Poor and good responders judged by physicians and patients*

	Poor responders (%)	Good responders (%)	Total (%)
Physicians (n = 44)			
Modafinil–placebo	31.82	20.45	52.27
Placebo–modafinil	11.36	36.36	47.73
Total	43.18	56.82	100.00
Patients (n = 46)			
Modafinil–placebo	30.43	21.74	52.17
Placebo–modafinil	15.22	32.61	47.83
Total	45.65	54.35	100.00

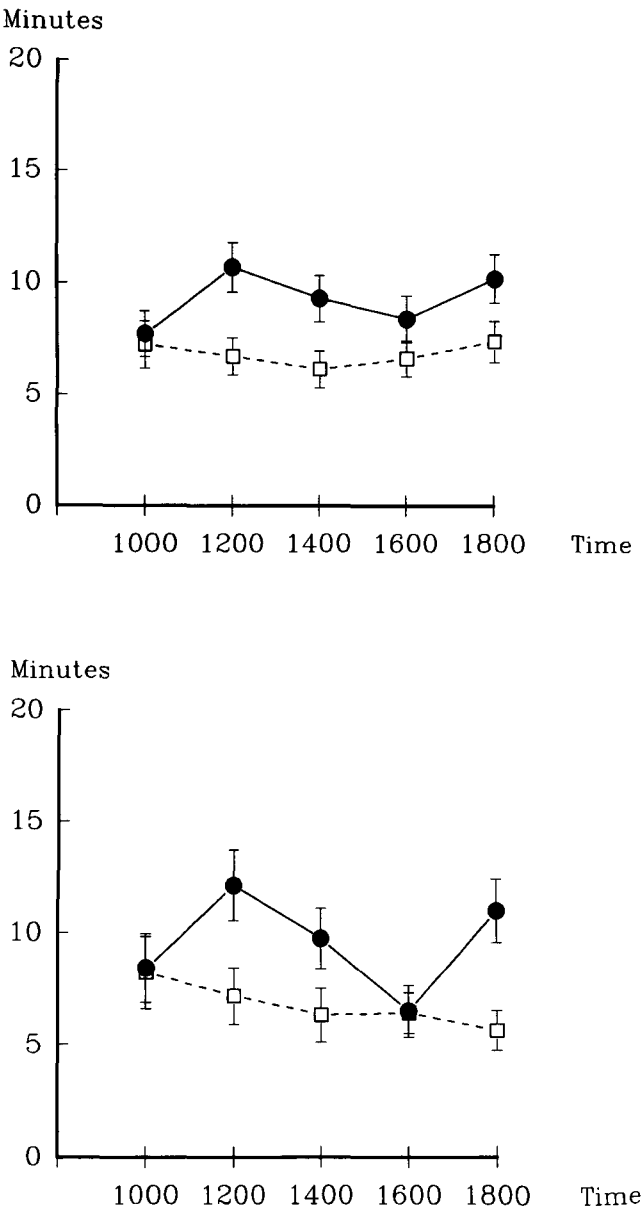

FIG. 1. Maintenance of wakefulness testing (MWT): profile of sleep latencies before (hollow squares) and after (filled circles) modafinil. Upper part of the figure: 43 subjects, including good and poor responders. Lower part of the figure: 23 good responders. Vertical bars represent standard error of the mean.

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TABLE 7. *Side-effects judged by physicians and patients*

	Placebo	Modafinil	Drug factor	
			F	p
Physicians (n = 45)	93.84 ± 7.43	85.42 ± 19.39	8.32	0.006
Patients (n = 46)	92.30 ± 9.12	83.43 ± 18.95	9.08	0.004

vigilance, but it also restores a normal circadian pattern of daytime vigilance (11).

Two of the main concerns with modafinil are the level of activity of the drug on excessive daytime sleepiness in comparison with amphetamines and whether or not it shows the same type of side effects. One review (8) has surveyed the results of 10 studies investigating the effects of nine different drugs used in the treatment of narcolepsy, including dextroamphetamine, methylphenidate and preliminary results of the present study concerning 21 subjects. According to this survey, modafinil ranked third, after dextroamphetamine and methylphenidate in producing clinically significant improvement. The results of our completed study confirm the preliminary results.

Two studies have investigated the differential effects of modafinil and d-amphetamine on sleep and early morning behavior in young healthy volunteers (12) and in elderlies (13). Both studies have shown a reduction of stage 2 sleep and REM sleep in subjects on d-amphetamine 20 mg, whereas night sleep was not modified on modafinil. Moreover, subjective sleep quality was impaired on amphetamine but not on modafinil. Our study confirms that the subjective quality of sleep is not modified on modafinil. Finally, evening and morning blood pressure and heart rate remained unchanged. This result is in agreement with our findings as well as with those of other studies (8,14,15).

Another finding was the absence of any significant effect of modafinil on cataplexy. This is to be compared with results of open studies showing positive effects of modafinil in a few subjects only (3–5).

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TABLE 8. *Peripheral effects (blood pressure and heart rate)*

	Placebo	Modafinil	Drug factor	
			F	p
Maximum blood pressure (reclining) (n = 42)	12.02 ± 1.55	11.69 ± 1.48	1.37	0.25
Minimum blood pressure (reclining) (n = 42)	7.26 ± 1.03	7.15 ± 1.11	0.38	0.54
Maximum blood pressure (standing) (n = 42)	12.17 ± 1.64	11.87 ± 1.52	1.23	0.27
Minimum blood pressure (standing) (n = 42)	7.90 ± 1.09	7.68 ± 1.27	0.08	0.77
Heart rate (reclining) (n = 42)	67.43 ± 9.61	67.83 ± 9.87	0.25	0.62
Heart rate (standing) (n = 40)	77.45 ± 10.56	76.65 ± 11.55	1.08	0.30

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