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Original article

Interest of modafinil, a new psychostimulant, during a sixty-hour sleep deprivation experiment

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Summary – Modafinil, a new psychostimulant, was evaluated in eight healthy volunteers subjected to 60 hours of sleep deprivation. During continued wakefulness, vigilance was evaluated by self-assessment questionnaires, analogue visual scales, multiple sleep latency tests (MSLT), sleep logs, and continuous ambulatory electroencephalographic recordings (EEG). Modafinil (200 mg) or a placebo was given every 8 hours for three days; the sessions were separated by a 15 day wash out period. Results indicated a satisfactory level of vigilance, both subjective and objective, after the administration of modafinil, characterised by the quasi total absence of microsleep episodes which gradually occurred under placebo conditions. The confirmed wakening potency of modafinil makes this substance suitable for therapeutic use in patients with sleep disorders such as Gelineau's syndrome and hypersomnia.

vigilance / sleep deprivation / EEG / MSLT / modafinil

INTRODUCTION

For approximately fifteen years, a new family of molecules called "eugregoric" (from the Greek eu: good, gregor: wakefulness), introduced by Bastuji and Jouvet (1988), have been synthesised in the L Lafon laboratory. Their principal pharmacological property is a wakening effect, moderate in the case of adrafinil (Olmifon®, Lafon) (Milhaud and Klein, 1985), and potent in the case of modafinil (Modiodal®, Lafon) (Duteil *et al*, 1990; Lagarde and Milhaud, 1990; Hermant *et al*, 1991; Lagarde, 1990). Modafinil has been evaluated for its wakening potency in animals (Lagarde, 1990; Duteil *et al*, 1990; Lagarde and Milhaud, 1990), achieving a continuous wakefulness for 96 hours without any behavioural disorders, and also in healthy volunteers participating in a moderate sleep deprivation experiment (Benoit *et al*, 1987; Puech and Bensimon, 1988; Bensimon *et al*, 1991). In addition to good quality wakefulness, psychomotor performance was also maintained at doses of 300 and 600 mg daily without any side effects. Considering this difference, adrafinil is frequently prescribed for impaired alertness, attention and ideomotor performance in the elderly (Guyotat, 1987; Laudet and Perilliat, 1987), while modafinil is intended more for pathological wakefulness disorders such as narcolepsy and hypersomnia (Bastuji and Jouvet, 1988; Carlander, 1994; Garma *et al*, 1986).

Since the effects of sleep deprivation are definitely negative and can cause a significant depreciation in psychomotor performance (Carskadon and Dement, 1981; Lagarde and Batejat, 1994a; Lagarde, 1991), we believed it would be worthwhile evaluating the efficiency of modafinil during a 60-hour sleep deprivation experiment using healthy volunteers. This paper specifically addresses vigilance and not the maintenance of performance which was recently considered by Lagarde and Batejat (1994b).

METHODS

Subjects

Eight healthy male volunteers participated in this experiment. Their age ranged from 22 to 31 years old

(mean age 27). Each subject met the requirements defined in the general experimental protocol submitted to the French Armed Forces Medical Service Ethics Committee. All subjects gave their written informed consent in accordance with the Helsinki Convention, and were free to withdraw from the experiment at any time.

Questionnaire and sleep log

Baseline data on the subject's morning sleep and evening sleep were determined by employing the Horne and Ostberg questionnaire (1976). A sleep log was maintained both during the sleep deprivation period and up to six days after to determine which nights corresponded to sleep recovery.

An analogue visual scale (Lagarde and Batejat, 1994a) was used prior to, during, and six days after sleep deprivation, each time at 08.00 hours. The subjective mood and vigilance self-evaluation scale which consisted of eleven items (drowsy, confused, relaxed, tired, clumsy, peppy, in good condition, depressed, anxious, sad, and happy), was presented as a one hundred millimetre analogue visual scale. For each item, represented by a grey area between 45 and 55 millimetres on the item line, the subject had to evaluate himself with respect to his typical state. The subjects were trained to fill out self-rating scales during a special training period one week preceding the start of the experiment.

Multiple Sleep Latency Test (MSLT)

Bearing in mind that modafinil is fundamentally a wakening substance and not an anti-sleep drug, tests were selected to assess the level of vigilance throughout the entire wakefulness period. This is why we used the MSLT and not the Maintenance of Wakefulness Test (MWT).

Experimental conditions for the multiple sleep latency test met the necessary requirements to provide interpretable results (Carskadon, 1986). The recording was obtained using the system recommended by Rechtschaffen and Kales (1968). It included a rolandic electro-encephalogram (C_3 and C_4), two horizontal and slanted right and left electro-oculograms, and an electromyogram of the chin. This system was augmented with a vertical EOG and an occipital EEG (O_1 and O_2) to observe the decrement in alpha activity during sleep latency. Electrode impedance never exceeded 10 kohms for all polygraphic recordings. Tests were run at 03.00, 09.00, 14.00, 17.00, and 22.00 hours, *ie* five times a day during the 60 hour sleep deprivation period, and on the day following the first night of recovery.

Ambulatory electroencephalography

For technical reasons ambulatory EEG was recorded on only four subjects. The equipment and signal processing methods have been described elsewhere (Le Menn *et al*, 1992). Essentially, it included a TEAC HR 30 J recording unit operating with audio type cassettes, a signal preamplifier for correct signal recording, and a box of rechargeable batteries providing the recorder a 24-hour operating capability. Signals were obtained from surface electrodes glued to the skin and fitted with low noise wiring. They were located so as to provide differential recordings from two EEG channels (C_3–C_z and O_1–O_2), an EOG channel, an EMG channel, and an EKG lead. An absolute time scale track was provided to the time data using a slow code generated by the recorder. EEG recordings began Tuesday at 07.00 hours and were terminated Thursday evening at 22.00 hours. Recordings were read on a TEAC MR 30 cassette reading unit using a TEAC TU 30 time decoder. Polygraphic recordings were visually processed according to the method developed by Rechtschaffen and Kales (1968).

Treatment

Dosages of 200 mg of modafinil (MODIODAL®): succinyl diphenyl methyl acetamide or a placebo, prepared by the Lafon laboratory, were administered three times a day (14.00, 22.00, and 06.00 hours) in a double blind study.

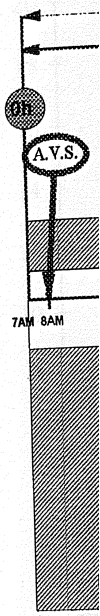
Protocol

Four subjects received modafinil or a placebo while the other four subjects were given a placebo or modafinil in a randomized order. During the record phase and allowing 15 days of wash out, the treatments were inversed.

Each experimental phase began on a Tuesday morning at 07.00 hours, after a normal night's sleep at the laboratory. During the periods when no measurements were made, subjects were observed by the experimenters and kept awake by various activities (watching TV, reading books, playing cards, *etc*) (cf experimental design, fig 1).

Statistical analysis

A Student test for small matched samples was used for the comparison of sleep latency times. Data obtained on the analogue visual scale and sleep log were submitted to an analysis of variance with repeated measures and, whenever possible, to a Newman-Keuls multiple means comparison test. Previously, the two paired cross-over trial test of Hills and Armitage (1979) had been used to evaluate the period factor and the interaction with treatment.



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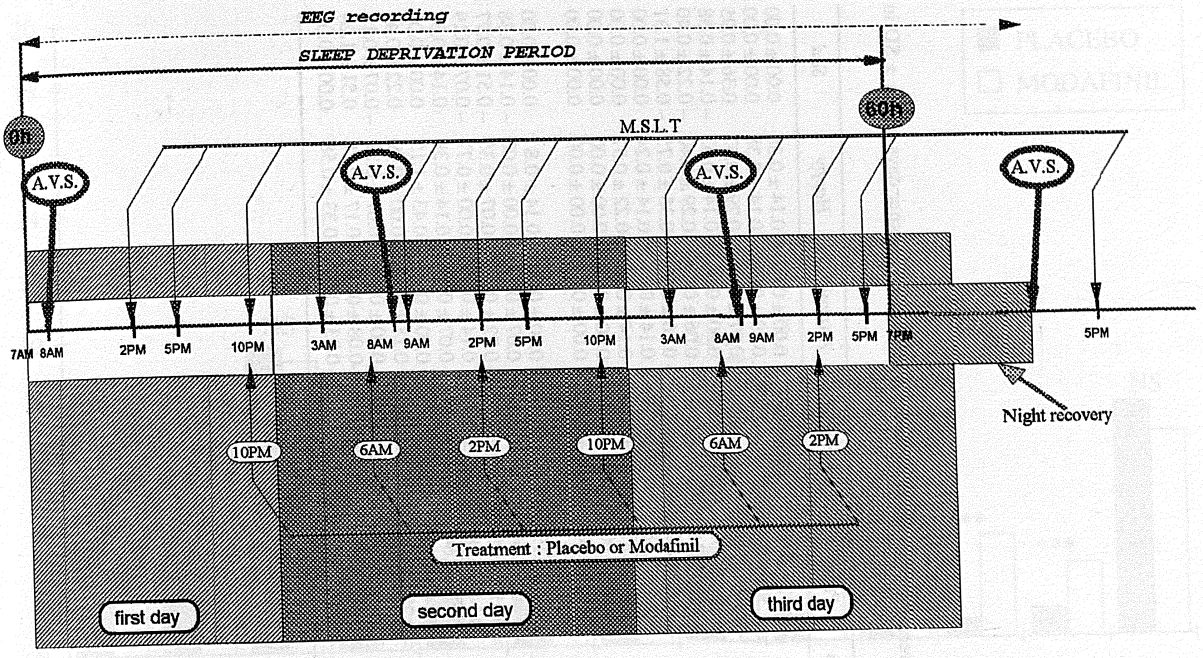

Fig 1. Diagram of experimental design during sleep deprivation period. AVS: Analog Visual Scale; MSLT: Multiple Sleep Latency Time; Treament: placebo or modafinil.

Table I. Sleep duration in placebo and modafinil situations. Statistical differences between post-treatment nights and pre-treatment nights; assessed using sleep log ($n = 8$). *: $p < 0.05$; **: $p < 0.01$ (mean ± SD in hours and minutes).

	Pre-treatment night	*Post-treatment night*					
		1st	*2nd*	*3rd*	*4th*	*5th*	*6th*
Placebo	6.53 ± 1.00	10.00 ± 1.46 *	8.10 ± 1.05*	0.94 ± 0.10*	8.31 ± 2.51*	8.07 ± 2.04*	8.00 ± 1.11*
Modafinil	7.03 ± 1.36	8.45 ± 2.34	10.05 ± 1.32**	9.20 ± 1.35*	8.32 ± 1.20*	8.05 ± 1.13*	7.07 ± 1.27

RESULTS

Subjects

Seventy-five percent of the subjects did not show any particular evening or morning preference, while twenty-five percent preferred mornings.

For most subjects, nocturnal sleep duration was 7–8 hours, for one particular subject it was only 6 hours. Sleep latency was less than 15 minutes except for two subjects, whose sleep latencies were 15–30 minutes and more than 30 minutes, respectively. Four subjects said they had a deep sleep, and the other four reported their sleep as variable.

Sleep log and behaviour analysis

The sleep log maintained by the subjects during the five days following sleep deprivation revealed a sleep rebound during the first recovery night ($p < 0.05$) in the placebo condition. A comparison with the pre-treatment night shows that the same phenomenon occurred with the modafinil condition but on the second night ($p < 0.01$). Sleep duration increased from the first to the fifth night in the modafinil condition ($p < 0.05$) and persisted after the sixth night in the placebo condition ($p < 0.05$) (table I). Two subjects had to take a diurnal nap on the second and third day after sleep deprivation in both situations.

A detailed behaviour analysis showed significant differences when using the placebo between responses on the first morning of sleep deprivation, used as reference, and responses obtained on the second day of sleep deprivation. Subjects reported having less energy ($p < 0.05$), being less relaxed ($p < 0.05$) and in worse condition

Table II. Data of mood parameters in placebo and modafinil situations. Statistical differences between the first day of sleep deprivation and the other days (mean ± SD in centimeters) ($n = 8$); *: $p < 0.05$.

		Relaxed	*Drowsy*	*Confused*	*Tired*	*Clumsy*	*Good condition*	*Peppy*	*Depressed*	*Anxious*	*Happy*	*Sad*
Placebo	J0	0.00 ± 0.00	0.22 ± 0.40	0.14 ± 0.24	0.50 ± 0.50	0.00 ± 0.00	−0.29 ± 0.39	−0.21 ± 0.39	0.07 ± 0.19	0.00 ± 0.00	−0.14 ± 0.38	0.00 ± 0.00
	J1	−0.27 ± 0.37	1.34 ± 1.14	0.98 ± 1.79	1.49 ± 1.12	0.73 ± 0.82	−1.02 ± 0.92	−1.30 ± 1.23	0.14 ± 0.2	0.29 ± 0.39	−0.14 ± 0.38	0.00 ± 0.00
	J2	−0.56 ± 0.45*	2.42 ± 1.84*	1.19 ± 1.88	2.43 ± 1.18*	0.51 ± 0.71	−1.59 ± 1.35*	−1.87 ± 1.56*	0.21 ± 0.39	0.07 ± 0.19	−0.29 ± 0.57	0.36 ± 0.95
	J3	0.00 ± 0.00	0.00 ± 0.29	0.29 ± 0.77	0.07 ± 0.78	0.15 ± 0.25	0.22 ± 0.90	0.08 ± 0.53	−0.14 ± 0.38	0.00 ± 0.00	0.14 ± 0.63	−0.14 ± 0.38
	J4	−0.14 ± 0.38	0.00 ± 0.29	0.00 ± 0.00	0.36 ± 0.38	0.00 ± 0.00	0.01 ± 0.44	−0.07 ± 0.18	−0.22 ± 0.40	−0.06 ± 0.73	0.29 ± 0.40	−0.22 ± 0.40
	J5	0.35 ± 0.61	0.00 ± 0.29	0.07 ± 0.78	0.00 ± 0.49	0.00 ± 0.00	0.01 ± 0.41	0.15 ± 0.25	−0.36 ± 0.75	−0.16 ± 0.95	0.35 ± 0.75	−0.58 ± 1.31
	J6	0.07 ± 0.45	−0.22 ± 0.40	0.07 ± 0.18	0.00 ± 0.29	0.07 ± 0.18	0.22 ± 0.56	0.14 ± 0.38	0.07 ± 0.19	0.14 ± 0.63	0.14 ± 0.24	0.00 ± 0.00
	J7	−0.07 ± 0.18	0.35 ± 0.47	0.07 ± 0.18	0.49 ± 0.55	0.00 ± 0.00	−0.28 ± 0.27	0.21 ± 0.81	0.00 ± 0.00	0.14 ± 0.38	0.22 ± 0.57	0.00 ± 0.00
	J8	0.00 ± 0.00	0.33 ± 0.61	0.00 ± 0.00	0.42 ± 1.04	0.00 ± 0.00	−0.09 ± 0.21	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
	J9	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	−1.00 ± 1.41	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Modafinil	J0	0.00 ± 0.49	0.21 ± 0.56	0.21 ± 0.39	0.36 ± 0.75	0.00 ± 0.00	−0.07 ± 0.19	−0.07 ± 0.19	0.00 ± 0.00	0.00 ± 0.00	−0.14 ± 0.8	0.00 ± 0.00
	J1	−0.21 ± 0.76	0.65 ± 0.96	0.29 ± 0.64	0.78 ± 1.29	0.50 ± 0.58	−0.74 ± 1.31	−0.80 ± 1.34	0.07 ± 0.45	0.07 ± 0.19	0.00 ± 0.00	−0.14 ± 0.38
	J2	−0.14 ± 1.04	0.86 ± 1.56	0.42 ± 1.44	0.94 ± 1.66	0.43 ± 0.60	−0.51 ± 1.50	−0.51 ± 1.53	−0.29 ± 0.77	−0.22 ± 0.40	0.07 ± 0.35	−0.51 ± 0.77
	J3	0.29 ± 0.92	−0.36 ± 0.96	−0.52 ± 1.59	−0.07 ± 0.67	0.07 ± 0.18	−0.08 ± 0.54	0.14 ± 0.48	0.00 ± 0.00	0.14 ± 0.38	0.00 ± 0.77	−0.07 ± 0.19
	J4	0.08 ± 0.46	0.07 ± 0.18	0.22 ± 0.27	0.14 ± 0.24	0.07 ± 0.18	−0.08 ± 0.54	−0.22 ± 0.64	−0.07 ± 0.18	0.07 ± 0.19	−0.14 ± 0.38	0.14 ± 0.38
	J5	−0.01 ± 0.52	0.06 ± 0.60	0.21 ± 0.39	0.07 ± 0.89	0.14 ± 0.38	−0.08 ± 0.89	−0.44 ± 0.62	0.00 ± 0.00	0.00 ± 0.00	−0.43 ± 1.15	0.00 ± 0.00
	J6	0.22 ± 0.40	0.14 ± 0.68	0.00 ± 0.57	0.21 ± 0.39	0.00 ± 0.00	−0.14 ± 0.63	−0.22 ± 0.41	0.15 ± 0.39	0.15 ± 0.39	0.00 ± 0.49	0.22 ± 0.40
	J7	0.36 ± 0.63	−0.14 ± 0.38	0.00 ± 0.00	0.07 ± 0.19	0.00 ± 0.00	0.28 ± 0.48	−0.15 ± 0.47	0.00 ± 0.00	0.00 ± 0.00	0.07 ± 0.19	−0.07 ± 0.18
	J8	−0.25 ± 0.62	−0.17 ± 0.41	0.00 ± 0.00	−0.34 ± 0.52	0.00 ± 0.00	0.17 ± 0.41	0.00 ± 0.00	0.68 ± 1.67	−0.08 ± 0.20	0.17 ± 0.41	0.51 ± 1.24
	J9	0.00 ± 0.00	0.00 ± 0.00	−0.50 ± 0.71	0.00 ± 0.00	0.00 ± 0.00	1.50 ± 2.12	0.00 ± 0.00	0.00 ± 0.00	−0.33 ± 0.58	0.33 ± 0.58	0.00 ± 0.00

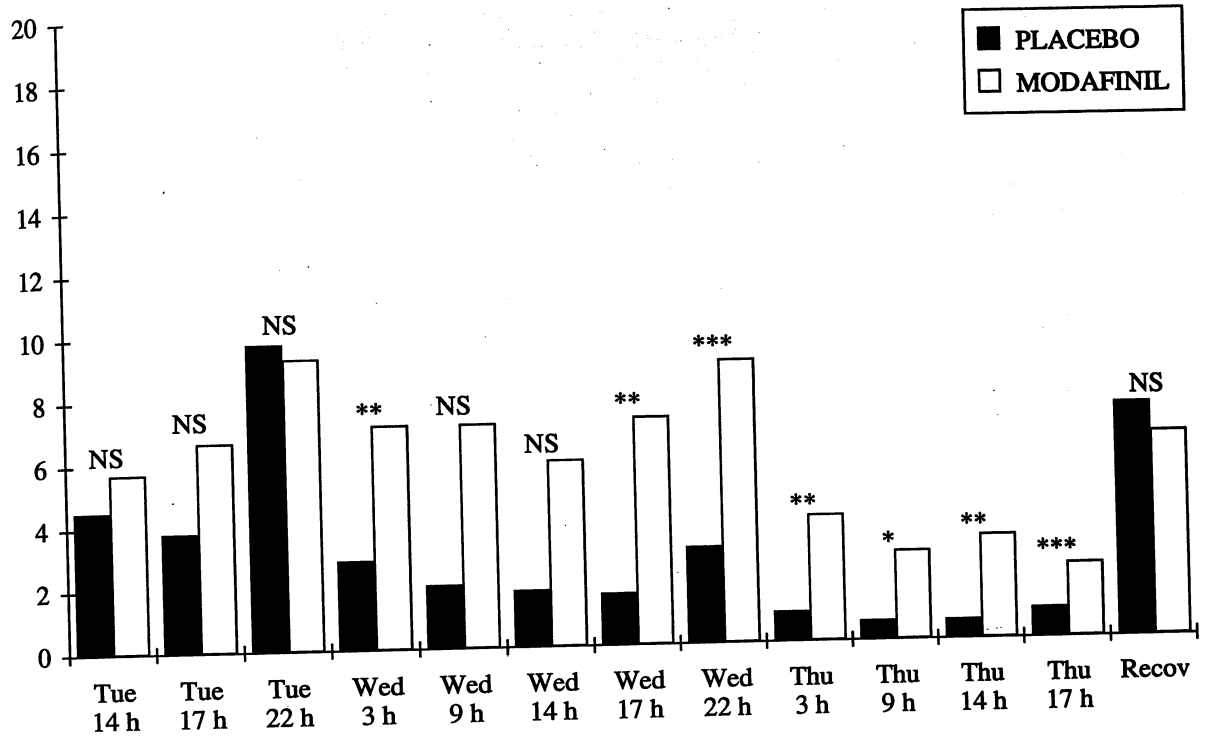

Fig 2. Sleep latencies obtained during the 60 hour sleep deprivation in placebo ■ and modafinil □ situation, by MSLT method. Observation of the fast decrease of sleep latencies with placebo and the maintenance of a good level of arousal with modafinil. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

($p < 0.05$). They were also sleepier after 24 hours of sleep deprivation ($p < 0.05$) and were more tired ($p < 0.05$). Recovery was rapid, on the very first day following termination of sleep deprivation.

No statistical difference was observed for the eleven criteria previously described, between the usual subjects' condition and their condition during sleep deprivation under modafinil treatment (table II).

Sleep latency

A detailed analysis of the MSLT during the 60 hours of sleep deprivation was previously reported (Lagarde and Batejat, 1994a). Briefly, we observed a significant and gradual decrease in sleep latencies as sleep deprivation was sustained. After 48 hours of continuous wakefulness, sleep latency times were reduced to less than one minute. The MLST administered at 17.00 hours on the day following the recovery night demonstrated a substantial increase in sleep latency time which was no longer statistically different from the MLST administered under the control conditions.

The first MSLT administered in the modafinil condition did not differ from those administered in the placebo condition because placebo sleep latency is not very different from control sleep latency. Nevertheless, sleep latencies rapidly became statistically different from placebo sleep latencies ($p < 0.05$, $p < 0.02$, and $p < 0.01$), illustrating an increase in vigilance (fig 2).

Microsleep episodes

A comparison of the two experimental conditions illustrates how the subjects responded differently to sleep deprivation.

A gradual increase in the number and duration of microsleep episodes was observed in the placebo condition from the outset of sleep deprivation. Episodes lasted 1–10 seconds and usually occurred at the same times.

The modafinil treatment on the other hand, suppressed microsleep episodes during the first 48 hours of sleep deprivation except in one subject who did exhibit a few brief moments of microsleep. No microsleep episodes were observed dur-

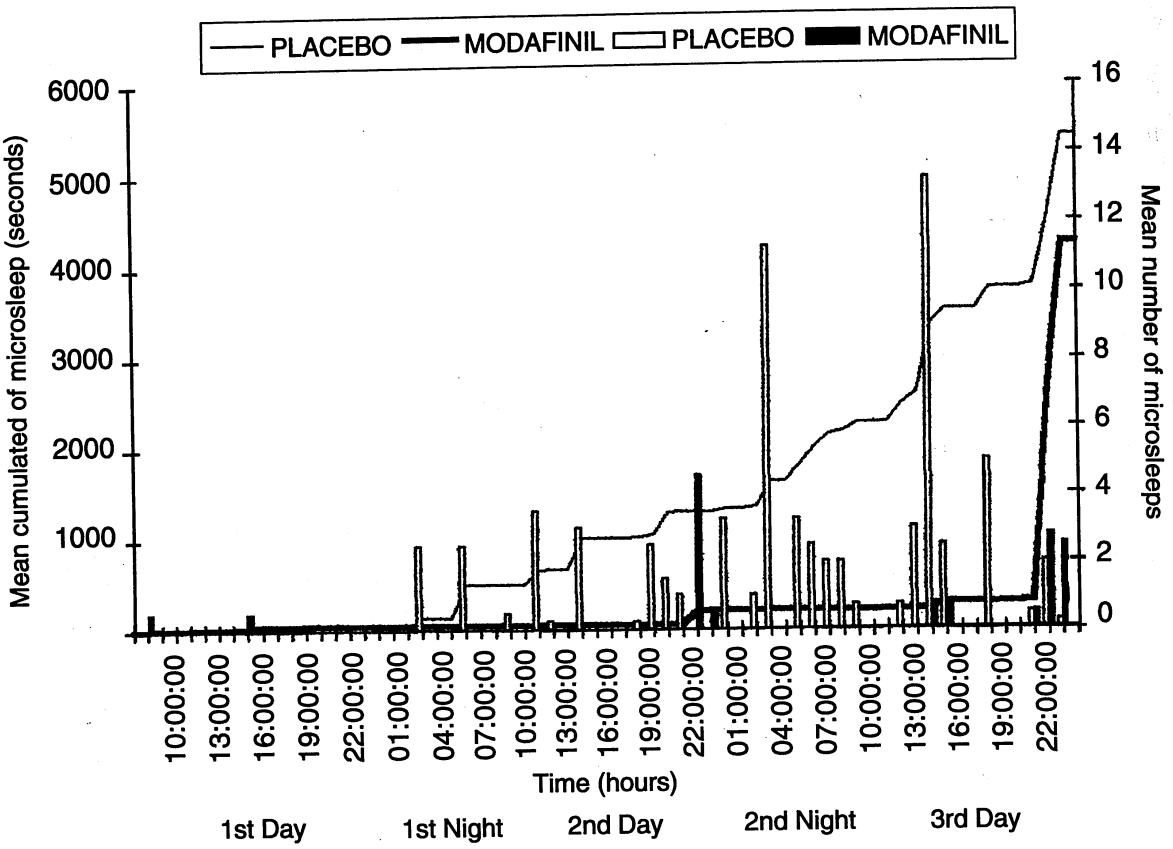

Fig 3. Number and duration of microsleeps during the 60 hour sleep deprivation in placebo and modafinil situations. Observation of a progressive increase of microsleep episodes in duration and frequency less important with modafinil than with placebo.

ing the second night in any of the four subjects treated with modafinil. During this period all subjects remained in a state of continuous wakefulness. Although, two brief periods of stage 1 sleep were observed in two of the subjects on the third day of the experiment at approximately 15.00 hours. We observed some relatively long microsleep episodes only after 60 hours of sleep deprivation, *ie* after 19.00 hours without renewed administration of modafinil.

DISCUSSION

This experiment, conducted on eight healthy volunteer subjects, was the first to have demonstrated the efficacy of modafinil during prolonged sleep deprivation. The behaviour analysis confirmed that sleep deprivation in the placebo condition created a general feeling of weariness, whereas the subjects using modafinil were less anxious and more dynamic and generally able to maintain their usual mental state. This effect, which could be qualified as "happiness", gave the subjects the ability to tolerate sleep deprivation much easier than subjects treated with a placebo. Studies in animals conducted by Simon *et al* (1992) demonstrated that the absence of anxiogenic effects after administration of modafinil, was contrary to what may be expected after administration of other psychostimulants such as betacarbolines, GBR, and amphetamines.

The potency of the wakening effect of modafinil could be objectively assessed by continuous ambulatory recording of the subjects' EEG. The quasi-total lack of microsleep episodes during modafinil treatments depicted the quality of wakefulness during the sleep deprived period. This was the first time that the microsleep suppressing effect of modafinil, during prolonged sleep deprivation, was demonstrated in man. The wakening potency of

modafinil has already been shown in animals (Lagarde, 1990) and in man (Bensimon *et al*, 1991; Benoit *et al*, 1987) but for shorter periods of time (24 or 36 hours). The innocuity of modafinil, particularly the maintenance of diurnal and nocturnal hypovigilance periods has been demonstrated, both in monkeys (Lagarde and Milhaud, 1990) and in man (Saletu *et al*, 1989), and was also confirmed by the MSLT.

The MSLT provided indications as to the effects of gradually diminishing sleep, marked by a significant reduction of sleep latencies after the 48th hour of total sleep deprivation, the condition corresponded to a "twilight zone" state of mentality. These effects on sleep latencies have already been reported in experiments on cumulated partial sleep deprivation episodes (Carskadon and Dement, 1981). Recovery of diurnal sleep latency similar to that of the baseline after one night's sleep suggests that one night's sleep following 60 hours of continuous wakefulness restores vigilance to a near normal level. The effect obtained after administration of modafinil is predominantly the maintenance of a higher level of vigilance, with sleep latencies always longer than those recorded in the placebo situation. It also proves that in a conductive environment a subject who has ingested a dose of modafinil (200 mg) can still fall asleep within 15 minutes. It is the wakening (not anti-sleep) effect of modafinil which distinguishes this substance from psychostimulants. For example, many sleep deprivation studies with similar protocols using the MSLT show a significant increase in sleep latency accompanied by frequent bouts of insomnia after the subjects have ingested 250 mg caffeine (Walsh *et al*, 1990; Zwyghuiszen-Doorenbos *et al*, 1990; Bonnet and Arand, 1992) or 20 mg of oral d-amphetamine sulphate (Newhouse *et al*, 1992), or 10 mg of methylphenidate and 37.5 mg of pemoline (Babkoff *et al*, 1992).

Analysis of the sleep logs has show that modafinil did not increase the recovery time of the subjects, in fact, it may have shortened it since the quantitative aspect of sleep was restored on the 5th night post-treatment, whereas, it remained high at the same point in time in subjects given the placebo. However, the sleep rebound observed after sleep deprivation only occurred on the second night post-treatment, perhaps due to the persistent effect of the modafinil molecule which may have accumulated in the body after several administrations. This hypothesis finds an argument in the dosage of modafinil and modafinil sulfone, an active metabolite, in plasma, which seemed to have a longer half-life. (Douce and Lagarde, 1992). We found an increased blood concentration of modafinil sulfone, from 0.09 mg/l 3 hours after the first administration of modafinil to 3.38 mg/l 3 hours after the sixth administration; the blood concentration of this metabolite remained high (2.8 mg/l) even 27 hours after the first recovery night. This could explain the need to sleep on the second night and not the first night post-treatment.

The high quality wakefulness obtained after the administration of modafinil to healthy subjects exposed to prolonged sleep deprivation, *ie* the wakening potency of this substance, has been demonstrated. This pharmacological substance has been used for several years, as an experimental treatment for cases of hypersomnia (Bastuji and Jouvet, 1988), with more than a 75% success rate (for review, see Lagarde, 1993). Additionally, it is used as a therapy for insomnia, to reinforce diurnal wakefulness (Garma *et al*, 1986). Moreover, it should be noted that modafinil seems to have other pharmacological properties, particularly neuroprotecting properties (Lagarde *et al*, 1993), and an anorexigenic effect which has been shown in rat studies (Nicolaidis and Saint-Hilaire, 1993). The suspected variety of pharmacological effects subtends a probably pluri-modal mechanism of action. Preliminary studies in the rat have indicated an indirect potentiating action of adrenergic alpha-1 synapses integrated in a central neuronal loop capable of stimulating vigilance (Duteil *et al*, 1990). The neuroprotecting action might involve a glutamatergic pathway, and the anorexigenic action a serotononergic pathway. However, for the time being, the fact that modafinil does not bind onto specific membrane sites restricts research to an indirect approach.

Studies on the subjective effects of modafinil as compared to amphetamines and caffeine using the Addiction Research Center Inventory (ARCI) and Profile Of Mood State (POMS) (Warot *et al*, 1992) yield results which are more suggestive of caffeine than of an amphetamine. Yet, the spectral EEG analysis of modafinil using Fast Fourier Transform (Lagarde *et al*, 1991) differs from the other psychostimulants such as, caffeine, amphetamine and tabernanthine, suggesting that modafinil appears to be an original molecule whose effect on the EEG spectrum is unique and which diffees from any of the currently used psychostimulants.

CONCLUSION

A sixty hour sleep deprivation experiment conducted using healthy volunteers demonstrated the

potency of the wakening effect of modafinil, a new substance which could be qualified as "eugregoric". This interesting pharmacological property has already found applications in pathology to treat Gelineau's syndrome and hypersomnias, and will perhaps be used in the near future in other areas. From a fundamental point of view, modafinil is a valuable pharmacological tool for studies on the wake-sleep cycle.

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