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SUCCESSFUL TREATMENT OF IDIOPATHIC HYPERSOMNIA AND NARCOLEPSY WITH MODAFINIL

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Abstract

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1. Modafinil, a putative central alpha 1 adrenergic agonist, was tested in idiopathic hypersomnia and narcolepsy.
2. Sleep attacks and drowsiness were significantly decreased in 83% of 18 hypersomniac subjects and 71% of 24 narcoleptics.
3. When cataplectic episodes were not totally suppressed the association of a low dose of Clomipramine was successful in improving them.
4. Modafinil, used for at least 3 years in some patients, produces, in most cases, no peripheric sides effects, does not disturb night sleep and is never responsable of tolerance of drug dependence.

Keywords: hypersomnia, modafinil, narcolepsy.

Abbreviations: improvement (IM), ineffectiveness (IN), not followed (NF), stop for side effect (SE).

Introduction

Classical treatment of hypersomnia consists in psychostimulants like amphetamines (Prinzmetal and Alles 1940, Yoss and Daly 1959, Passouant et al 1964) associated with tricyclics if cataplexia is present (Akimoto et al 1960, Takahashi 1976). These stimulants, which are not always effective, generally produce tolerance and drug dependence.

Adrafinil (Olmifon^{R}), a central alpha 1 adrenergic agonist (Rambert et al 1986), is being used in France to improve wakefulness and attention in geriatric patients. We have tested the effect of modafinil, a similar alpha 1 adrenergic agonist with a stronger arousing effect, on a selected population of idiopathic hypersomniac and narcoleptic patients.

Methods

Subjects

24 narcoleptics (7 women and 17 men, mean age = 40 $\pm$ 15 years)and 18 idiopathic hypersom

niacs (8 women and 9 men, mean age = 45 ± 15 years) were included in this study. For each subject the clinical diagnosis was confirmed by a 24 hours polyhypnographic record before treatment.

Drugs

Modafinil was administered in the morning and at noon. The oral dose varied from 200 to 500 mg/day according to the patient weight and the severity of the symptoms.

Daytime sleepiness and sleep attacks were evaluated by comparing sleep diary data before and after treatment. Sleep diary technique has been previously described (Bastuji and Jouvet 1985). For the evaluation of the mean number of drowsiness and sleep attacks per day, weighted values were used when pooling the datas of all the subjects.

Statistical analysis

Analysis of variance (ANOVA) was used to compare drowsiness and sleep attacks during the control period and the first and second month of treatment.

Results

Idiopathic Hypersomnia (Fig 1 and 2)

Three patients were not followed up. One of them presented some side effects (sialorrhea). In the other 15 patients with idiopathic hypersomnia the number of drowsiness and sleep episodes during daytime was significantly reduced by modafinil. During the second month of treatment drowsiness diminished from 3.33 ± 0.66 (mean ± SEM) to 1.33 ± 0.34 episodes per day (Student t test, $p < 0.05$) while sleep episodes were reduced from 1.28 ± 0.33 to 0.25 ± 0.06 episodes per day ($p < 0.01$). This represents a mean decrease of 60% and 80% respectively. Improvement was evident from the beginning of treatment, but the highest degree of significance was obtained on the 2nd month. In most subjects, only the usual nap after lunch time was not suppressed. In 6 subjects modafinil was discontinued after 6-12 months of treatment and total absence of symptoms has persisted since then, for at least one year after the interruption of the treatment.

Narcolepsy (Fig 1 et 2)

In the 22 followed up narcoleptic patients sleep attacks were reduced from 1.98 ±0.22 (mean ± SEM) to 1 ± 0.21 episodes per day ($p < 0.001$) and drowsiness from 3.43 ± 0.34 to 1.63 ± 0.21 episodes ($p < 0.001$).

Modafinil was effective in reducing or eliminating the symptoms in 17/24 narcoleptics (71%):

- there was a total disappearance of both sleep attacks and cataplexia in 1 patient whose treatment was started few months after the onset of the disease.
- the 16 other patients were improved with regard to sleep attacks and drowsiness but in 6 of them cataplectic episodes were not totally suppressed; in such cases, the

association of a low dose of clomipramine (10-20 mg/day) was sufficient to reduce cataplexia whereas, when used alone, higher doses of this drug (40-60 mg/day) were necessary to control cataplectic attacks but did not suppress drowsiness or sleep attacks.

In 4 patients with a long narcoleptic history (10 years or more) or in whom cataplectic episodes were very frequent (5 or more daily), modafinil was ineffective in cataplexia and only slightly improved drowsiness and sleep attacks.

Side effects induced interruption of modafinil in one patient after 2 months of successful treatment.

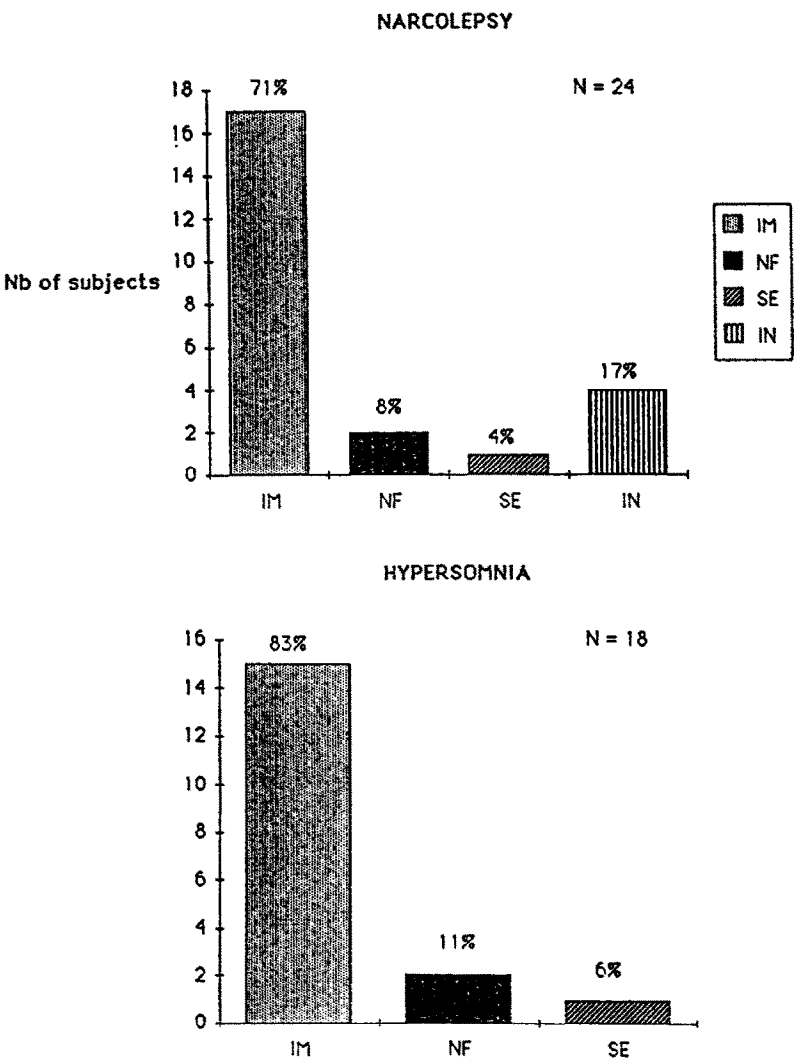

Fig 1. Results of treatment with modafinil in narcoleptics and in hypersomniac patients. IM = improvement, NF = not followed up after 1 or 2 months, SE = stop for side effect, IN = ineffectiveness.

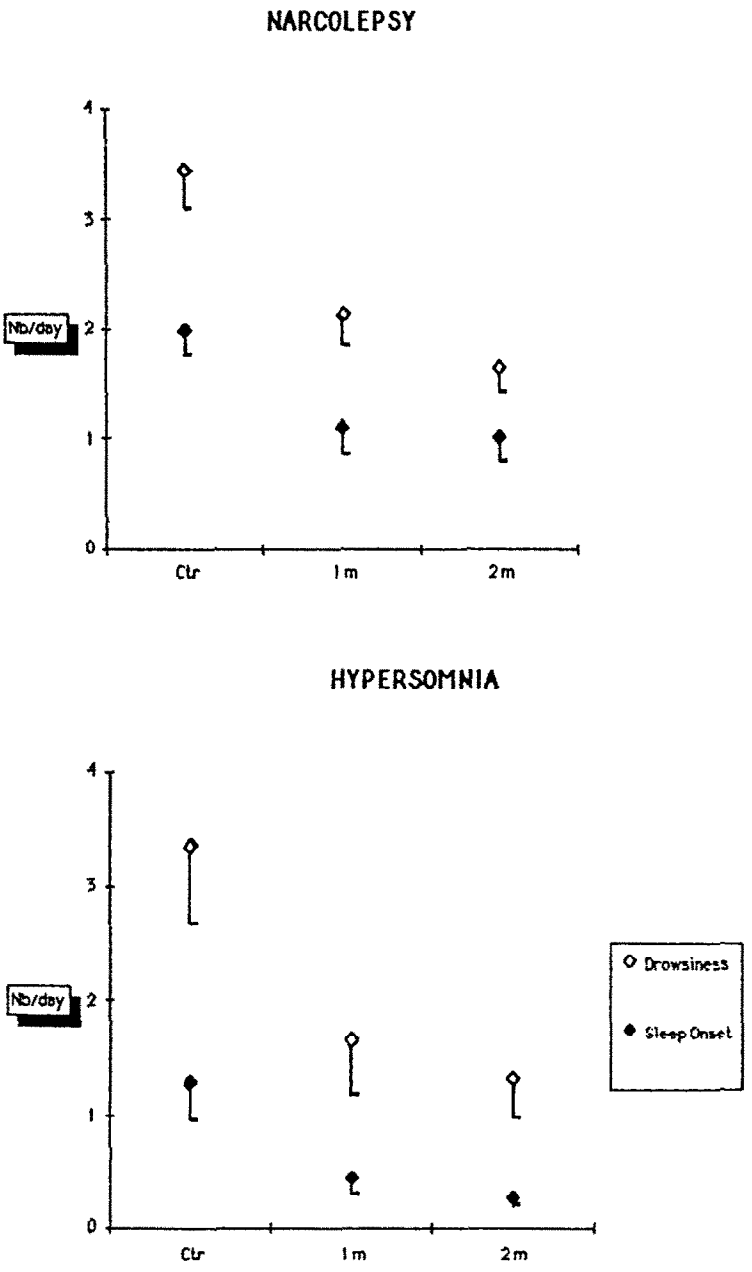

Fig 2. Comparison of mean number of drowsiness and sleep attacks per day before treatment, on the first and on the second month of treatment with modafinil in 22 narcoleptic and 15 idiopathic hypersomniac patients (ANOVA = $P < 0.05$). Ctr = Control, 1m = First month, 2m = Second month of modafinil, vertical bars = S.E.M.

Tolerance

In most cases (92%), modafinil produced no side effects, even when administered during 2 or 3 years. With this drug we have never observed tolerance or dependence phenomena, nor night sleep disturbance. Conversely, narcoleptic patients frequently reported an improvement of dysomnia: their nocturnal sleep became more stable and refreshing.

Another important fact is that a massive dose of this drug does not seem to have dramatic consequences. Indeed one patient, a 21 years old female, attempted to commit suicide by ingesting 45 tablets of 100 mg of modafinil. She was hospitalized 9 hours after the ingestion, too late to undergo a gastric washing. Blood concentration of modafinil was 8.85 mg/l, whereas the maximal concentration of modafinil in control subjects taking 200 mg per day during 2 weeks is 3.8 mg/l. Except for tachycardia, clinical examination and biological tests were normal. She fully recovered after 24 hours of excitation, nausea and total insomnia.

Conclusion

Modafinil, a putative central alpha 1 adrenergic agonist, appeared to be of real interest for the treatment of idiopathic hypersomnia and narcolepsy. Drowsiness and sleep attacks were significantly reduced with this drug in a group of 18 hypersomniac subjects and 24 narcoleptics. Modafinil may sometimes not totally suppress cataplectic episodes; in these cases it is useful to associate a low dose of clomipramine (10-20 mg/day).

Modafinil, used for more than 3 years in some of our patients, produced no peripheral side effects in most cases. Interestingly enough modafinil did not disturb nocturnal sleep and was not responsible of tolerance or drug dependence.

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