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Original article

Subjective effects of modafinil, a new central adrenergic stimulant in healthy volunteers: a comparison with amphetamine, caffeine and placebo

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Summary – The subjective, behavioral and physiological effects of modafinil (300 mg PO) a new central adrenergic stimulant, were compared with those of dextroamphetamine (15 mg PO), caffeine (300 mg PO) and placebo in a randomized double-blind cross-over study. Sixteen healthy volunteers participated in the study y: 8 males and 8 females with no history of drug abuse and moderate use of caffeine. Subjective and behavioral effects were studied using the Addiction Research Center Inventory (ARCI), Profile of Mood States (POMS) and Visual Analog Scales before and 1, 2, 4 and 8 h post single oral dosing. Results showed that subjective effects of modafinil (300 mg) differed markedly from those of dextroamphetamine (15 mg). They were close to those produced by caffeine (300 mg). These results indicate that modafinil (300 mg) does not possess amphetamine-like subjective effects in a healthy population. If subjective feelings are related to drug abuse liability, it could be assumed that modafinil, at the dose used in therapeutics, does not possess any abuse liability comparable to amphetamine.

modafinil / amphetamine / caffeine / healthy volunteer / subjective effects / ARCI

Introduction

Studies of drugs of abuse in humans have focused on evaluating the behavioral and subjective effects of these drugs in drug-experienced subjects and normal human volunteers (Johanson *et al*, 1983; Johanson *et al*, 1987; Schuster 1989; Jasinski and Henningfield, 1989). Studies have been conducted with a variety of drugs, including opiates (Jasinski *et al*, 1970), benzodiazepines (Johanson and Uhlenhuth 1980 a, b; Tewes and Fischman, 1982), amphetamines (Martin *et al*, 1971; Johanson and Uhlenhuth 1980 a, b; Tewes and Fischman 1982; Miller and Griffith 1983; Chait *et al*, 1986, 1988; Heishman and Henningfield 1991; Kelly *et al*, 1991) and other psychostimulants (Fischman 1989; Fischman *et al*, 1976; Stern *et al*, 1989). The purpose of these investigations was to provide a complete pharmacological profile of these drugs to be used as standards of comparison. The extent to which other drugs share characteristics would provide a basis for predicting their abuse potential.

Modafinil is a new drug characterized by an increase in nocturnal and behavioural arousal in monkeys (Hermant *et al*, 1991). It increases locomotor activity in mice without inducing stereotyped behaviour (Duteil *et al*, 1990). Its action may be linked to modulation of central alpha1 adrenoceptors (Rambert *et al*, 1990).

Data concerning reinforcing properties of modafinil in animals are not yet available. Studies in mice indicate that modafinil can induce tolerance phenomenon, the mechanism of which could be enzyme induction. Following cessation from one week chronic administration, there is no evidence to suggest a withdrawal syndrome in mice and monkeys (unpublished data: Lafon Laboratories: Brochure for Investigators). In man, modafinil is indicated in narcolepsy and idiopathic hypersomnia (Bastuji and Jouvet, 1988). Considering that drugs increasing wakefulness, for example amphetamine, can be drugs of abuse, the abuse liability of modafinil is a matter of great concern.

The explicit assumption of this study is that the

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more similar a drug is to a known drug of abuse, in terms of its subjective and physiological effects, the more likely the drug is to be abused.

We compared modafinil to amphetamine because it is a well-known drug of abuse, which can induce dependence and tolerance phenomena. Caffeine, an ubiquitously and regularly used psychostimulant, was chosen as a second comparator. Its subjective and reinforcing effects have been extensively studied (Griffiths and Woodson, 1988).

Materials and methods

Subjects

Sixteen volunteers (eight female, eight male), 19-34 years of age (mean 23.94) participated in the study. They were physically healthy and no abnormalities were found on clinical examination, standard ECG and laboratory measures of haematology, blood biochemistry and HIV and B hepatitis serology. None had histories of mental illness, sleep disturbances or pathological anxiety. All had Minimult, Eysenck Personality Inventory and Cattell 16 PF scores within the normal range. Before the study, volunteers were tested for the presence of illicit drugs in urine (benzodiazepines, opioids, cannabinoids, amphetamine and cocaine). Subjects were informed as to what type of drugs they would receive during the study. Written informed consent was obtained from each volunteer and the study was approved by the Ethical Committee of the Pitié-Salpêtrière Hospital. Five subjects had some experience with psychoactive drugs (psychostimulants and cannabinoids), but none had a history of any type of drug abuse or dependence with the exception of tobacco dependence. Subjects' habitual caffeine intake was not used as a criterion for acceptance: the only requirement was some prior use of caffeine through caffeine containing beverages, with no unusual reactions related to caffeine effects. Current medication (excluding contraceptive pills), alcohol and caffeine consumption, and driving motor vehicles were prohibited on experimental days.

Experimental design

Subjects acted as their own control and received each treatment at weekly intervals in a double-blind crossover study according to a randomized balanced schedule derived from a Latin square. On test days, subjects arrived at 8 am, they had a standard breakfast without coffee or tea. They ingested the capsule under observation by the experimenter. Test sessions began at 9 am, before drug administration (T0) and 1 (T + 1 h), 2 (T + 2 h), 4 (T + 4 h) and 8 h (T + 8 h) later. They had lunch at 1 pm at the hospital. They were free to leave the department at 5.30 pm.

Drugs and dosages

Bensimon *et al* (1991) demonstrated that 200 mg of modafinil antagonised the psychomotor and cognitive impairment induced by 36 h sleep deprivation in healthy subjects. The dosage recommended in patients is from 100 mg to 200 mg bid (Bastuji and Jouvet, 1988). Amphetamine 15 mg and caffeine 300 mg are demonstrated to be single active doses on subjective assessment in a healthy population and also well tolerated (Tewes and Fischman 1982; Stern *et al*, 1989). The caffeine dose is roughly equivalent to three strong cups of coffee. Modafinil 300 mg, d-amphetamine sulfate 15 mg, caffeine 300 mg and placebo were administered in identical opaque gelatin capsules.

Measurements

Subjective effects

They were assessed using three different types of questionnaires.

Addiction Research Center Inventory (ARCI) (Hill *et al,* 1963 a, b)

The ARCI is a true-false (1-0) questionnaire with empirically-derived scales that are sensitive to the effects of a variety of classes of abused drugs (Haertzen, 1966, 1974). The short version of the ARCI consists of 49 items which have been separated into five clusters described as measuring typical drug effects such as stimulant-like (Amphetamine, A scale and Benzedrine Group, BG scale), euphoric (Morphine-Benzedrine Group, MBG scale), sedative (Pentobarbital-Chlorpromazine-Alcohol Group, PCAG scale) and dysphoric (LSD scale).

Profile of Mood States (POMS) (Mac Nair *et al,* 1971)

The version of the POMS we used consists of 65 adjectives describing momentary mood states. Subjects indicate how they feel at the moment in relation to each of the 65 adjectives on a 5-point scale from "not at all" (0) to "extremely" (4). We have studied six scales of items empirically separated using factor analysis (anxiety, depression, anger, vigor, fatigue and confusion). The value of each scale is determined by adding the numbers checked for each adjective in that scale.

Visual Analog Scales (VAS)

Ten centimeter-line Visual Analog Scales were used to rate mood on anxious, tired, happy, relaxed, drowsy, dizzy, clumsy, alert, energetic, sad and depressed dimensions (Warot *et al*, 1989).

Drug-liking. At the end of each experimental day, volunteers were asked whether they would like to take another time, the drug they were administered in the morning. The answer was "yes" or "no".

Sleep questionnaire. The morning following each experimental day, at awakening, volunteers had to answer a nine-item sleep questionnaire (Bensimon *et al*, 1990).

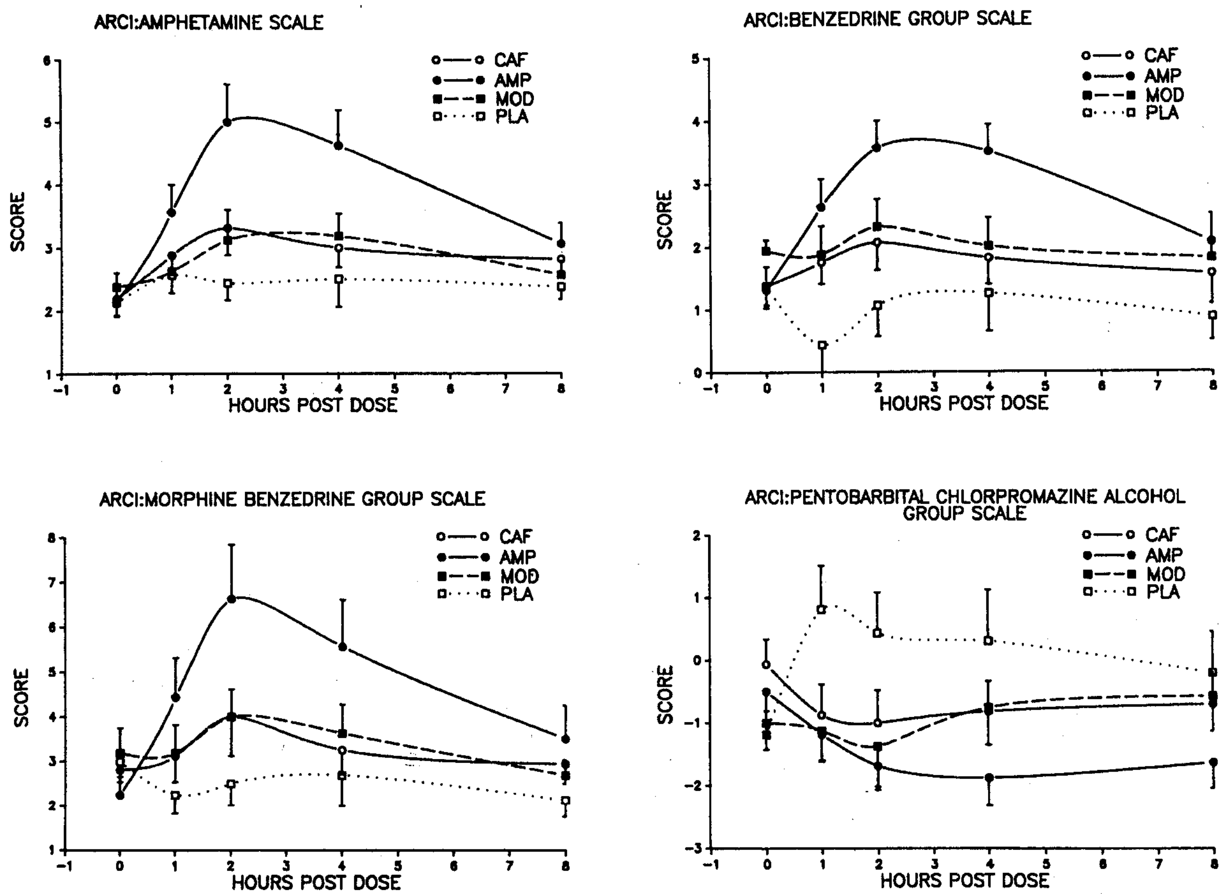

Fig 1. Mean scores (± sem) for the ARCI scales before 1, 2, 4 and 8 h following treatments.

Physiological measures. Heart rate and systolic diastolic blood pressure were recorded on supine (10 min resting) position by a Dinamap recorder.

Adverse effects. They were recorded by free interviews at each time of evaluation, and during the wash-out period.

Statistical analysis. Statistical analysis was performed using BMDP-2V and SAS programmes. Continuous variables (ARCI, POMS, Visual Analog Scales and haemodynamic parameters) were analyzed by repeated-measures (ANOVA). The factors included were treatment, day of experiment, subject and time of evaluation and the interactions tested were time × subject, time × day, time × treatment. A drug effect was considered significant if either a main effect of treatment or a time × treatment interaction was obtained. Between treatment comparisons were handled by MANOVA and *t* tests were carried out using the Bonferonni probabilities to adjust for the number of comparisons. Non parametric tests were carried out for ordinal data (sleep and drug-liking questionnaire) *ie* Friedman test and Wilcoxon sign rank test for paired comparisons, or McNemar's test.

Results

All subjects completed the study over the 4-week period.

Subjective effects

ARCI

Responses to the ARCI scales are illustrated in figure 1.

ANOVA indicated significant treatment effect and time × treatment interaction for four of the five ARCI subscales: A [$F(1,3) = 5.36$; $P = 0.003$

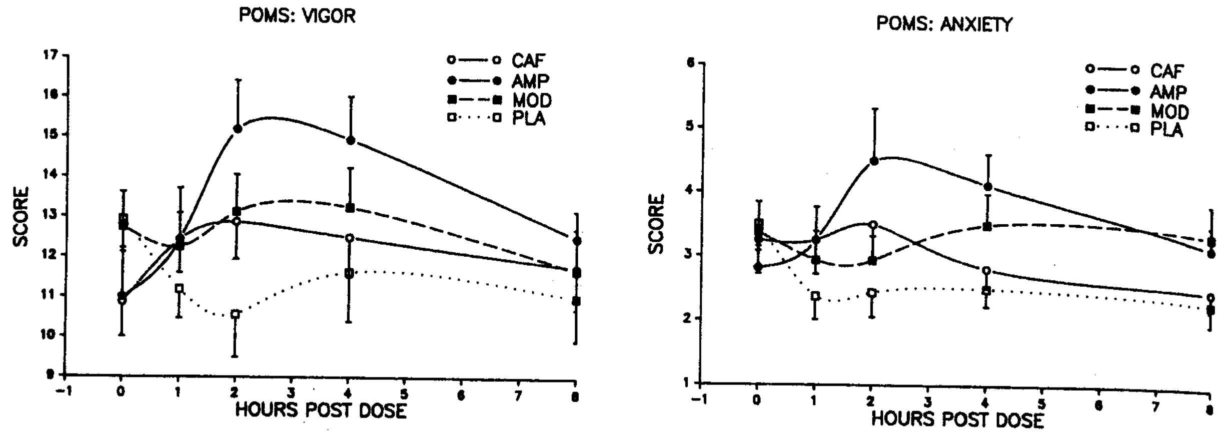

Fig 2. Mean scores (± sem) for the POMS subscales: tension-anxiety, vigor before 1, 2, 4 and 8 h following treatments.

and F(4,12) = 3.07; *P* = 0.0006], BG [F(1,3) = 6.13; *P* = 0.0015 and F(4,12) = 2.17; *P* = 0.015], MBG [F(1,3) = 4.42; *P* = 0.008 and F(4,12) = 3.44; *P* = 0.0002], PCAG [F(1,3) = 3.19; *P* = 0.03 and F(4,12) = 1.87; *P* = 0.04]. The LSD subscale was not significantly modified by the treatment. Between treatment comparisons showed that amphetamine differed significantly from placebo for the four ARCI subscales. Amphetamine increased significantly the scores for A [F(1,15) = 13.40; *P* = 0.002], BG [F(1,15) = 12.88; *P* = 0.003], MBG [F(1,15) = 9.91; *P* = 0.007] and decreased the scores for PCAG [F(1,15) = 8.89; *P* = 0.009]. On the A subscale, the increase was significantly more important with amphetamine than with modafinil [F(1,15) = 7.45; *P* = 0.02]. On the BG subscale, modafinil significantly increased the scores compared to placebo [F(1,15) = 5.98; *P* = 0.03]. No difference between caffeine and placebo, modafinil and caffeine could be evidenced on the four ARCI subcales. When significant differences were observed, they were located 2 and 4 h post-dosing, less regularly 1 or 8 h following treatment administration.

POMS

Results obtained on the POMS are presented in figure 2.

ANOVA showed significant treatment effect and time × treatment interaction on subscales "anxiety" [F(1,3) = 2.83; *P* = 0.05 and F(4,12) = 1.89; *P* = 0.038] and "vigor" [F(4,12) = 2.53; *P* = 0.004]. Compared to placebo, amphetamine increased significantly the scores for these two subscales [F(1,15) = 7.84; *P* = 0.01 and F(1,15) = 10.26; *P* = 0.006], the maximum effect taking place 2 and 4 h following treatment. There was also a non-significant trend for modafinil, and to a lesser extent for caffeine, to increase "vigor".

Visual Analog Scales

ANOVA evidenced significant treatment effect and/or a time × treatment interaction for items: "tired" [F(1,3) = 4.41; *P* = 0.008 and F(4,12) = 1.83; *P* = 0.0046], "happy" [F(4,12) = 3.84; *P* = 0.0001], "relaxed" [F(4,12) = 2,42; *P* = 0.006], "drowsy" [F(1,3) = 4.97; *P* = 0.005], "alert" [F(1,3) = 3.76; *P* = 0.017 and F(4,12) = 2.25; *P* = 0.01], "energetic" [F(1,3) = 4.54; *P* = 0.007 and F(4,12) = 2.66; *P* = 0.002], "sad" [F(4,12) = 3.5; *P* = 0.0001], and "depressed" [F(4,12) = 2.08; *P* = 0.02].

Between treatment comparisons indicated that the subjects felt significantly less "tired" and "drowsy", more "energetic" and "alert" than usual following amphetamine compared to placebo [F(1,15) = 11.07; *P* = 0.005; F(1,15) = 10.28; *P* = 0.006; F(1,15) = 10.27; *P* = 0.006; F(1,15) = 6.95; *P* = 0.02] and modafinil [F(1,15) = 10.85; *P* = 0.005; F(1,15) = 11.84; *P* = 0.004; F(1,15) = 5.28; *P* = 0.04; F(1,15) = 4.83; *P* = 0.04]. Significant differences were observed 1 h (T + 1 h), 2 h (T + 2 h) and 4 hours (T + 4 h) following treatment administration.

The adjectives "happy" and "sad" differentiated amphetamine from placebo and modafinil in the between treatment comparisons analysis, 2 h post-dosing (T + 2 h).

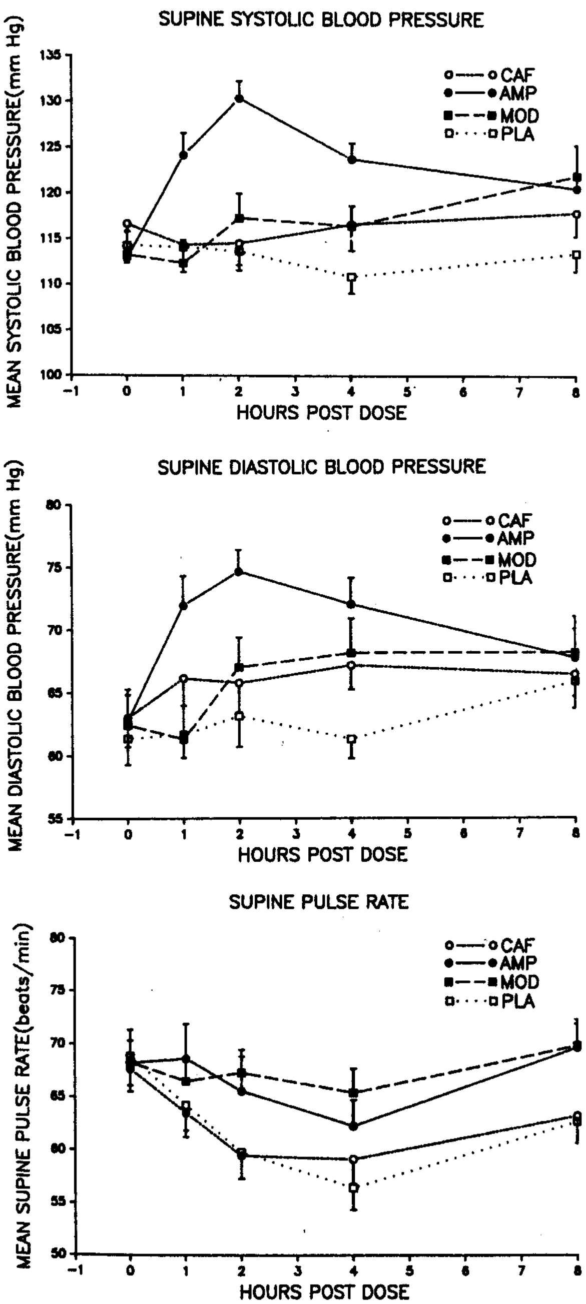

Fig 3. Time action curves for supine systolic, diastolic blood pressures, heart rate (m ± sem).

Drug liking

Eleven subjects with amphetamine, four subjects with caffeine, three subjects with modafinil and two subjects with placebo answered that they would like to take another dose of the drug in the future. Amphetamine was significantly different from the three other drugs: placebo [Khi^2 (1 df) = 7.4; P= 0.007], modafinil [Khi^2 (1 df) = 8; P = 0.005)] and caffeine [Khi^2 (1 df) = 7; P = 0.008)]. There were no significant differences between caffeine and placebo, modafinil and placebo, modafinil and caffeine.

Sleep questionnaire

The sleep questionnaire results showed significant differences between the four treatments only on the first question, namely "did the treatment help you to sleep?" (Friedman test, Khi^2 (1 df) = 9.24; P = 0.02). For the question "Time to fall asleep compared to usual", there was a tendency but it did not reach the significance level. The between treatment comparisons indicated that modafinil (P = 0.07) badly influenced nocturnal sleep compared to placebo and that sleep induction was longer than usual compared to placebo following modafinil P = 0.03) and amphetamine (P = 0.02).

Haemodynamic parameters (figure 3)

ANOVA indicated significant treatment effect and time × treatment interaction for the three haemodynamic parameters in supine position: systolic blood pressure [F(1,3) = 16.28; P = 0.0001 and F(4,12) = 6.35; P = 0.0001], diastolic blood pressure [F(1,3) = 9.25; P = 0.0001 and F(4,12) = 4.26; P = 0.0001] and heart rate [F(1,3) = 7.93; P = 0.0003 and F(4,12) = 2.32; P = 0.01]. On these three parameters, amphetamine was significantly different from placebo, increasing supine systolic [F(1,15) = 70.94; P = 0.0001] and diastolic [F(1,15) = 32.98; P = 0.0001] blood pressures. Increased systolic blood pressure and heart rate following modafinil administration were significantly different from placebo.

Placebo and caffeine tended to decreased heart rate while modafinil and amphetamine did not.

Side effects

Five subjects with amphetamine, five subjects with modafinil and one subject with caffeine experienced a sensation of intellectual efficiency. Nine subjects with amphetamine, four subjects with modafinil and three with caffeine had a sensation of awakening. Five subjects with amphetamine, four subjects with modafinil and three with caffeine had a sensation of internal tension. Eight subjects with amphetamine and four subjects with modafinil experienced a sensation of loss of appetite. Three subjects with amphetamine, eight subjects with modafinil and two with caffeine experienced a moderate transient headache.

Discussion

The purpose of the present study was to determine whether subjective effects of modafinil were similar to those of dextroamphetamine, a well known drug of abuse, and to those of caffeine, which is another psychostimulant.

Modafinil showed no sedation (PCAG scale), no pronounced elation or euphoria (MBG scale), increased sensation of energy and intellectual efficiency (BG scale) and very few somatic or dysphoric effects (LSD scale). Modafinil was clearly differentiated from amphetamine on the A scale. This scale has been shown to be sensitive to the dose-response effects of psychostimulants and was developed for the specific purpose of distinguishing amphetamine-like drugs from other psychotropic drugs (Martin *et al*, 1971). The observed changes in this study on the ARCI with amphetamine and caffeine are qualitatively similar to those reported by other authors with the same drugs, in human healthy volunteers (Tewes and Fischman 1982; Chait and Griffiths 1983; De Wit *et al*, 1985; Chait *et al*, 1986, 1988; Stern *et al*, 1989), and in drug addicts (Martin *et al*, 1971; Fischman *et al*, 1976; Fischman and Schuster, 1982; Miller and Griffith, 1983; Heishman and Henningfield, 1991). However, compared to the above mentioned reports made in relation to drug addicts, the present study performed in healthy volunteers provided qualitatively and quantitatively similar significant changes, but with a much lower dose. These results also demonstrate that studies evaluating subjective effects of drugs could be conducted likewise with subjects without histories of drug abuse, at least with this particular class of drugs.

The responses to the POMS pointed out that modafinil and caffeine were not significantly different from each other, amphetamine and placebo. Amphetamine was significantly different from placebo on "vigor" and "anxiety" subscales. These results are in line with those reported in the literature as expected effects. On the "vigor" subscale, our results with amphetamine are in agreement with those reported in previous studies carried out on human healthy volunteers treated with doses ranging from 5 mg to 10 mg (Johanson *et al*, 1983; Chait *et al*, 1986, 1988). On the "anxiety" subscale, our findings with amphetamine are similar to those published by Johanson *et al* (1983) and Chait *et al* (1986), using 10 mg amphetamine. In the former study, significant decreases in "fatigue", "confusion" and "depression" were reported with amphetamine. Such results have not been observed in our study. Caffeine tended to increase scores on the anxiety subscale without any effect on "vigor" and "fatigue" subscales, whereas Stern *et al* (1989) found with similar doses, significant changes in the expected direction (*eg* increased ratings of stimulation and anxiety). With doses from 400 to 800 mg of caffeine, Chait and Griffiths (1983) described significant increases in "anxiety".

The results on the Visual Analog Scales pointed out that amphetamine was significantly different from placebo for five items: subjects were less tired and drowsy, more alert and energetic and more relaxed. These feelings could be linked to well-known amphetamine properties: stimulation and well-being. This last result has been previously described by Martin *et al* (1971), as a paradoxical effect. However, this effect might be related to the euphoriant action of amphetamine. Modafinil was significantly different from amphetamine on many items ("relaxed", "drowsy", "alert", "energetic", "happy", "sad", and "depressed") suggesting that modafinil does not induce well-being and euphoriant effects at the dose studied.

The analysis of "drug-liking" results showed that amphetamine was significantly different from the three other treatments, indicating that if subjects had to take the drug on another occasion, they would choose amphetamine rather than modafinil, caffeine or placebo.

The results observed on the sleep questionnaire, while not always reaching statistical significance, showed that modafinil and amphetamine affect sleep parameters: increased sleep latency and shortened sleep duration.

The pressor effect observed after dextroamphetamine replicates data reported by Martin *et al* (1971) and Miller and Griffith (1983). Our results did not evidence peripheral sympathomimetic effects on supine heart rate. Side effects we noticed with amphetamine are already known. The incidence of headache observed in this sample under modafinil is higher than in the placebo condition, which is not in accordance with clinical data (Phase I studies, Bastuji and Jouvet, 1988). We have no definite explanation, except that the collection of side effects might differ from one study to another.

Our findings strongly suggest that, on the one hand, modafinil and amphetamine at the dose studied have different profiles of subjective effects, and on the other hand, modafinil and caffeine at the dose studied have slightly different profiles of subjective effects. Modafinil (300 mg) and amphetamine (15 mg) produced very close levels of stimulant effects in the present study, but amphetamine increased scores of mood scales often associated with dependence (*eg*, euphoria, well-being).

The main finding of this study, in accordance with preliminary animal data, suggests that modafinil (300 mg) induced subjective effects which do not resemble amphetamine 15 mg subjective feelings. In a therapeutical situation, modafinil might not possess amphetamine abuse liability. However, the results of this study do not enable us to predict the way drug abusers might use modafinil. Obviously, it would have been more suitable to establish a dose-response curve with modafinil to ensure that amphetamine-like effects would not appear with higher doses. However, repeated administration of potential drugs of abuse in a healthy population raised ethical considerations.

Further clinical trial data in patient populations and post-marketing drug surveillance programmes would provide more information concerning this specific problem with modafinil.

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