

SCIENCE NEWS NOTE

Modafinil: The Unique Properties of a New Stimulant

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Modafinil, a novel stimulant which has several remarkable features that distinguish it from other stimulants, has been developed by Lafon, a French pharmaceutical company. Unlike the amphetamines, for example, modafinil is reported to have minimal peripheral side effects at therapeutic doses. It also appears to have a low abuse potential, does not interfere with normal sleep, and does not seem to produce tolerance. It improves vigilance especially in sleep-deprived subjects. It has been used clinically for up to 3 years in the treatment of narcolepsy and idiopathic hypersomnia. It could be an ideal replacement for amphetamine in short-term operations in which fatigue might threaten the successful completion of a mission. We recommend that military laboratories experienced in studying sustained performance include modafinil or perhaps a more selective alpha 1 receptor agonist in their investigations.

THE ABILITY of aircrew to sustain performance when faced with the multiple stresses inherent to aviation has long been a concern of aviation medicine. The use of medications to enhance aircrew sleep has been important in recent military operations in both the Falklands Campaign (22) and in the 1986 Libyan Air Strike (30). Amphetamines were also used by USAF aircrew during the Libyan Air Strike as a countermeasure to fatigue. Although occasionally used operationally, amphetamines have serious limitations such as cardiovascular side effects, interference with sleep, psychiatric disturbances, and addiction. Caffeine, widely used by aircrew to enhance vigilance, is also not without side effects such as irritability, diuresis, and tremor.

A novel stimulant called modafinil has been developed which has several remarkable features that distin-

guish it from amphetamine. Modafinil (2-[(diphenylmethyl)sulfinyl]acetamide) (32) is a centrally active alpha 1 adrenergic agonist produced by Lafon Labs of Maisons-Alfort, France (Fig. 1). During a press conference at an international defense meeting in France, Professor Michel Jouvet, an international authority on sleep, claimed that modafinil has potential military application since it has many characteristics which would make it preferable to the amphetamines as a stimulant medication (31). He asserted that modafinil "could keep an army on its feet and fighting for three days and nights with no major side-effects." Unfortunately, there are few studies in the scientific literature to support these claims. In fact, most of the available information about the compound has come from nonarchival sources such as abstracts and posters presented at European scientific meetings. In the following brief review, the pertinent citations for the compound are highlighted.

Pharmacological Specificity

The central adrenergic properties of the compound at moderate doses in mice (128 mg/kg) were demonstrated by blocking the behavioral effects with prazosin (a selective alpha 1 antagonist) which were not blocked by the more peripherally active alpha blocker, phentolamine, or by the beta blocker, propranolol (9,26). However, at subtoxic doses in rhesus monkeys (more than 40 mg/kg) behavioral stereotypy (circling) is seen and the compound demonstrates dopaminergic effects in that this behavior can be blocked by pimozide (a dopamine antagonist) but not by prazosin (20). There may be some question as to specificity since other researchers (8) report that at high doses (708 mg/kg) neither yohimbine (a selective alpha 2 antagonist) nor prazosin could block the inhibitory effect of modafinil on pancreatic secretion. However, most of the evidence for modafinil's receptor binding characteristics seems to support the compound's effect on central adrenergic receptors. For example, repeated dosing with modafinil increases the number of prazosin binding sites in rat brain (25) suggesting alpha 1 adrenergic up regulation.

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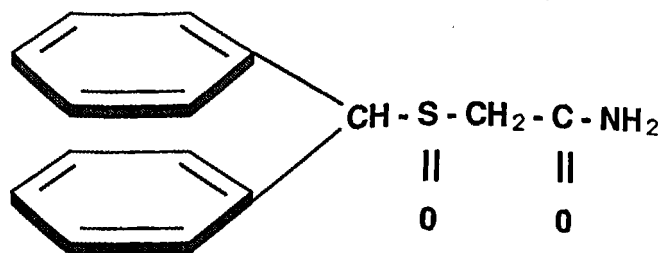


Fig. 1. Chemical structure of modafinil.

Unfortunately, no other data are currently available for the receptor specificity of modafinil.

Dosage and Toxicity

In mice, modafinil induced an increase in locomotor activity at threshold dose of 8 mg/kg (26). In rhesus monkeys, 12 mg/kg increased alertness for a 9-h period and 45 mg/kg kept the monkeys continuously awake during a 12-h night session (21). In humans, modafinil exhibited maximum vigilance enhancing properties peaking 4 h after a dose of 200 mg (28).

Minimal animal toxicity and a wide therapeutic window is typically observed with modafinil. LaGarde described an experiment in which monkeys were kept alert and active for over 70 h without side effects by oral doses of 22.5 and 45 mg/kg (20). No rebound or residual effects were observed at the end of the treatment. In rats, doses up to 400 mg/kg for 1 month and 200 mg/kg for 3 months demonstrated no toxic effects. The LD-50 in mice and rats was reported to be 1250 mg/kg (28). In dogs, doses up to 75 mg/kg for 3 months showed only hypermotility and stereotyped behavior. Doses of 200 mg/kg for 2 months caused hypermotility with exhaustion and several fatalities (28). Modafinil appears to have a low abuse potential since it is not self-administered by animals (20). Human data, however, are limited to uncontrolled studies on a limited number of patients.

Toxicity in humans is likewise minimal. Some studies have found no side effects (11,12,13), whereas others have found occasional mild side effects such as headache or nausea (18,19), moderate tachycardia (17), or hypersalivation (2). Pulse and blood pressure changes were not usually observed at normal therapeutic doses (3,27,28,29). Unlike amphetamines, even bedtime doses of 100–200 mg did not significantly interfere with sleep (3,10,27). Tolerance is not typically observed (3,29). Interestingly, two subjects noted an improved libido (28). One study reported no side effects at doses up to 600 mg in adults, and only insomnia with a 700 mg dose. Side effects in elderly patients included delayed sleep, insomnia, euphoria, and slight motor excitation at doses above 500 mg (28). In another study, 32 narcolepsy/hypersomnia subjects were safely maintained on 100–300 mg modafinil for 3 to 45 months (mean 21 months) (6). In a third study, 38 out of 42 patients had no side effects on 200–500 mg/d—some of these patients were maintained on modafinil for up to 3 years (3). The relative safety of massive doses of the drug was demonstrated by an attempted suicide in which 4,500 mg were ingested by a 21-year-old female; side effects were limited to only tachycardia, excitation, and insomnia (3).

Performance Research

The peer-reviewed documentation regarding the behavioral properties of modafinil is sparse. It is particularly important to determine the effects of repeated dosing, given the behavioral toxicity associated with chronic administration of the amphetamines. In mice, the compound appears quite safe. According to one report, large doses of modafinil (256 mg/kg) did not produce stereotypic movements nor did it produce peripheral sympathetic stimulation typical of other stimulants (26).

Three controlled, double-blind studies have evaluated the performance effects of modafinil in healthy adults. The first evaluated the effect of a morning dose of 200 mg on electroencephalogram (EEG) indicators of vigilance and daytime sleep latency. This study found decreased EEG indications of fatigue (theta/alpha ratio)—similar to those observed with d-amphetamine—following 200 mg, but did not find any behavioral changes from a placebo control (15–17). Another study, following the morning administration of 200, 400, and 600 mg of modafinil, demonstrated enhanced concentration, complex reactions, mood, affectivity, cognitive function, and increased critical flicker frequency threshold with a paradoxical decrease in psychomotor activity (28). These effects were maximal after the 200 mg dose. A third study demonstrated that a 200-mg nighttime dose of modafinil in sleep-deprived volunteers reduced subjective sleepiness and improved performance on search and memory tests (4,5).

Sleep Disorders

By far the most research with modafinil has been done on sleep research. One investigator believes that it may, in fact, be the best available treatment for narcolepsy and cataplexy (23). However, only two controlled, double-blind studies evaluating its efficacy have been reported. In the first of these, Laffont demonstrated that 200 mg of modafinil decreased the number of sleep attacks and diurnal yawning in narcolepsy and idiopathic hypersomnia (18,19). The second double blind study addressed the use of modafinil in alcoholic brain syndrome (29). An improved clinical outcome and normalization of EEG changes were demonstrated over a 6-week period.

Several additional investigators have described the results of the treatment of narcolepsy, idiopathic hypersomnia, and insomnia with modafinil in uncontrolled studies. Modafinil seems to be very effective in narcoleptics and hypersomniacs in improving daytime vigilance while not interfering with nocturnal sleep (1–3,14,24). In 1988, Bastuji and Jouvet reported on the treatment of 42 narcolepsy and hypersomnia patients; 17 out of 24 narcoleptics (71%) and 15 out of 18 hypersomnia patients (83%) responded favorably to treatment (1,2,3). Regular daytime treatment for as long as 3 years with at least 200 mg of modafinil in narcoleptics has produced neither tolerance nor drug dependence in these patients. Billiard treated patients with 100–300 mg daily of modafinil for up to 45 months; 31 out of 47 narcolepsy patients (66%), and 4 out of 7 hypersomnia patients (57%), had a favorable response to treatment

(6,7). Picard reported favorable results in 12 out of 17 narcoleptics (71%) treated with an average dose of 200 mg (24). In another study, 10 out of 11 (91%) narcoleptics responded favorably to treatment with 100–300 mg of modafinil (12,13). Garma noted a subjective improvement in wakefulness but no significant change in sleep latency. Garma and Levy also used 100–200 mg modafinil daily in the daytime treatment of “tiredness” due to insomnia; 8 out of 11 (73%) patients responded favorably (13,14).

DISCUSSION

Modafinil has been discussed in European scientific meetings since 1986. There may be a better compound developed in the interim; a more potent compound might be suggested by the relatively large dose levels required to produce typical behavioral effects (200 mg) when compared to other stimulants. It is possible that a compound with greater receptor potency is available, as modafinil has been an investigational new drug for 4 years. However, it may be that the sparse side effect profile of modafinil derives from its slow or incomplete receptor occupancy. Unfortunately, no reports regarding the binding characteristics for modafinil have been found.

Besides the enormous potential for a safe and effective anti-fatigue agent in the military, modafinil could be used by civilians in critical jobs involving night shift work. Transportation workers, emergency services personnel, public utility workers, and astronauts are only some of the most visible groups in which extended duty cycles are often required. Pharmaceutical houses expend only a limited amount of resources in stimulant research, since the market is restricted by legal issues and drug abuse liability. However, the development of modafinil brings to light a crucial social question. What would be the impediment for its use if a compound such as modafinil is more like caffeine than amphetamine in terms of safety, and yet as effective as the amphetamines? Virtually no information is available in the peer-reviewed scientific literature regarding long term use of the substance in normal subjects to guide such a decision. We have concluded, however, that enough data have been set forth to recommend that the compound be seriously considered for further research, particularly in laboratories set up to measure sustained performance effects of medications in fatigued but otherwise healthy individuals.

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