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Pharmacology, Biochemistry and Behavior 82 (2005) 133 – 139

PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR

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Cognitive effects of modafinil in student volunteers may depend on IQ

Delia C. Randall [a,b], John M. Shneerson [b,*], Sandra E. File [a]

[a] *Psychopharmacology Research Unit, Centre for Neuroscience Research, King's College London, London, UK*
[b] *Respiratory Support and Sleep Centre, Papworth Hospital, Cambridge, UK*

Received 1 February 2005; received in revised form 3 June 2005; accepted 22 July 2005
Available online 2 September 2005

Abstract

The results of two previous studies on the effects of modafinil, a selective wakefulness-promoting agent, in healthy university students were combined in a retrospective analysis. This allowed determination of whether the effects of modafinil were dependent on IQ and whether the larger sample size ($n=89$) would reveal more cognitive benefits. A battery of cognitive tests was completed 2–3 h after dosing. In the whole sample, modafinil (200 mg) significantly reduced the number of missed targets in a test of sustained attention (RVIP). However, interestingly, several interactions between modafinil and IQ emerged. Modafinil (100 and 200 mg) significantly improved target sensitivity in the RVIP test, but only in the group of 'lower' IQ (mean $\pm$ sem $=106\pm0.6$), not in the 'higher' IQ group (mean $\pm$ sem $=115.5\pm0.5$). Furthermore, there were significant modafinil $\times$ IQ interactions in two further tests. Modafinil significantly reduced speed of responding in a colour naming of dots, and in clock drawing, but only in the 'lower' IQ group. Thus, the cognitive benefits of modafinil seem particularly marked in tests of vigilance and speed, in which sleepiness would be an important factor. Furthermore, the results indicate that high IQ may limit detection of modafinil's positive effects.

Keywords: Modafinil; Cognition; IQ; Sleepiness; Wakefulness

1. Introduction

Modafinil 2-[(diphenylmethyl)sulfinyl]acetamide was originally licensed for the treatment of excessive daytime sleepiness (EDS) in narcolepsy, but the licence now also includes EDS in obstructive sleep apnoea/hypopnoea syndrome (OSAHS) and chronic shift-work sleep disorder. It has also been reported to have some cognitive benefits in certain clinical conditions. In patients with narcolepsy, accuracy was improved in tests of speed (Boivin et al., 1993; but see Broughton et al., 1997) and sustained attention (Hirshkowitz and Harsh, 2004). In OSAHS patients, modafinil reduced the frequency of lapses of attention and improved reaction times in the Psychomotor Vigilance Task (Dinges and Weaver, 2003; but see Kingshott et al., 2001). A rather different pattern of cognitive improvement was reported in adults with attention deficit/hyperactivity disorder (ADHD), where modafinil was reported to improve Digit Span, pattern recognition memory, spatial planning and stop-signal motor inhibition (Turner et al., 2004a). Modafinil was also found to improve Digit Span and attentional set-shifting in schizophrenic patients (Turner et al., 2004b). It is thus possible that the pattern of cognitive benefits resulting from modafinil depend on the disorder, with improvements in vigilance and speed of responding being most marked in disorders of sleepiness, and improvements in memory and executive function being most marked in disorders of dopaminergic function.

In sleep-deprived healthy adults, modafinil counteracted the cognitive impairments resulting from sleep loss (Bensimon et al., 1991; Lagarde and Batejat, 1995; Pigeau et al., 1995; Stivalet et al., 1998; Caldwell et al., 2000; Wesensten et al., 2002; Wesnes and Macher, 2004). Many of the tasks that showed positive effects of modafinil included attentional and reaction time components.

* Corresponding author. Respiratory Support and Sleep Centre, Papworth Hospital, Cambridge, CB3 8RE, UK. Tel.: +44 1480 830541; fax: +44 1480 364568.
E-mail address: john.shneerson@papworth.nhs.uk (J.M. Shneerson).

0091-3057/$ - see front matter
doi:10.1016/j.pbb.2005.07.019

More recently, modafinil has received publicity in the general press for its use as a potential cognitive-enhancer and thus its effects in volunteers who are not sleep-deprived are of particular importance. In a group of high IQ (mean 115) university students, Randall et al. (2003) failed to detect any positive effects on cognitive performance of modafinil (100 and 200 mg) and Liepert et al. (2004) found no effects of modafinil (200 mg) on the performance of a small battery of tests (reaction time, nine-hole-peg and letter cancellation tasks) in healthy male subjects (mean age 27 years, IQ not specified). In a group of high IQ (mean 118) middle-aged volunteers, modafinil (200 mg) improved performance in a simple speed test (colour naming of dots) and in a clock-drawing test (Randall et al., 2004). Using a somewhat different range of tests, and combining the data for the 100 and 200 mg doses, Turner et al. (2003) found that modafinil improved performance of a high IQ (mean 115) group of young men (mean age 25 years) in the Digit Span, Pattern Recognition Memory (PRM), Stop-Signal Reaction Time and spatial planning (New Tower of London) tests. Finally, Randall et al. (2005) found that modafinil improved performance in a group of students (mean IQ 109) in Digit Span (100 mg), PRM (100 and 200 mg), colour naming of dots (200 mg) and in a test of sustained attention (Rapid Visual Information Processing, RVIP; 200 mg). Müller et al. (2004) found that the positive effects of modafinil (200 mg) in students (IQ not specified) were limited to two relatively difficult and monotonous computerised working memory tests.

Thus, there is some consistency in the tests in which improvements have been found in young adults who are not sleep deprived and, although they include simple speed tests and sustained attention, they are not restricted to these and include tests of short-term and working memory. It is, however, possible that the high IQ of the groups studied has limited detection of positive effects of modafinil. In the Müller et al. (2004) study, the difficult manipulation condition of a numeric working memory task showed positive effects of modafinil, but only in the poorer performing students. Similarly, Mehta et al. (2000) noted that the positive effects of methylphenidate (40 mg) on spatial working memory performance were greatest in those volunteers with lower baseline working memory capacity. In a study of the effects of ginkgo biloba in healthy young adults, Stough et al. (2001) found improved performance in the Trail-Making Test A only in the half with the lower verbal IQ. If modafinil is a cognitive enhancer, then it might well be expected that its effects would be more readily detected at levels of lower performance, where there is likely to be more scope for improvement. The purpose of the present study was to investigate this possibility by combining the data from our two previous student volunteer studies, thus providing a sample size ($n = 89$) large enough to divide the group according to IQ.

A second advantage of this meta-analysis is that it allows us to determine whether additional effects of modafinil will be detected with a larger sample size. The two studies that found no effects both used small samples: $n = 30$ in a parallel-groups design (Randall et al., 2003) and $n = 10$ in a crossover design (Liepert et al., 2004). The studies that did detect positive effects used sample sizes from 45–60 in parallel-groups designs (Randall et al., 2004, 2005; Turner et al., 2003) and 16 in a crossover design (Müller et al., 2004). If inadequate sample sizes have been limiting the detection of some effects, then this analysis should reveal additional actions of modafinil that might help to clarify the pattern of its cognitive benefits.

2. Methods

2.1. Subjects and drug

This is a retrospective analysis of 89 healthy, non-sleep-deprived student volunteers (47 men and 42 women, aged 19–23 years), who had been recruited from King's College London to our double-blind, parallel-groups studies of the effects of modafinil on cognitive performance (Randall et al., 2003, 2005). The studies were approved by King's College London Research Ethics Committee. All subjects gave written informed consent and they were paid £10 for participating. The screening procedure, including exclusion criteria, is described in detail by Randall et al. (2003, 2004). On the day of cognitive testing, subjects received 100 or 200 mg modafinil (Cephalon Inc, West Chester, PA, USA) or placebo, in two unmarked capsules, each of which contained lactose or 100 mg modafinil (formulated by St Thomas' Hospital Pharmacy). Volunteers were asked to abstain from alcohol the day before testing and from caffeine 3 h before the test session. Because nicotine abstinence has been shown to impair cognitive performance in smokers (Snyder and Henningfield, 1989; Hasenfratz and Battig, 1993), subjects were not asked to abstain before the testing session. Eleven subjects smoked (4 in the placebo group, 4 in the 100 mg and 3 in the 200 mg). Cognitive testing was carried out 2–3 h after dosing in order to coincide with peak plasma concentration of modafinil of 2–4 h after oral ingestion (Robertson and Hellriegel, 2003).

The National Adult Reading Test-II (NART-II; Nelson and Willison, 1991) was used to obtain an estimate of verbal IQ. Subjects were allocated to one of two groups: 'lower' IQ (≤ 110; $n = 42$; mean IQ = 106.1, SEM = 0.6; 19 male, 23 female) and 'higher' IQ (≥ 111; $n = 47$; mean IQ = 115.5, SEM = 0.5; 28 male, 19 female).

2.2. Cognitive tasks

The computerised tests were taken from the Cambridge Neuropsychological Test Automated Battery (CANTAB; Cambridge Cognition, Cambridge, UK), and are described in detail by Sahakian et al. (1989) and Owen et al. (1990, 1991). The pen-and-paper tests are described in detail by