Modafinil Elicits Sympathomedullary Activation

Indu Taneja, Andre Diedrich, Bonnie K. Black, Daniel W. Byrne, Sachin Y. Paranjape, David Robertson

Abstract—The autonomic effects of modafinil (Provigil), a psychostimulant widely used to attenuate fatigue and promote wakefulness, are currently unexplored. We assessed the effect of modafinil on autonomic nervous system. We compared oral modafinil (400 mg×1) versus placebo in 12 healthy hospitalized normal subjects in a randomized double-blind, placebo-controlled cross-over study for 3 days each with subjects in 150 mEq sodium, 70 mEq potassium balance at the Vanderbilt General Clinical Research Center. Modafinil increased resting heart rate (9.2±2.0 bpm; mean [±SE]; 95% confidence interval [CI], 4.7 to 13.6; P=0.001), resting systolic blood pressure (7.3±3.2 mm Hg; 95% CI, 0.2 to 14.4); P=0.044), and resting diastolic blood pressure (5.3±1.7 mm Hg; 95% CI, 1.4 to 9.1 mm Hg; P<0.012). Modafinil elicited a 42% higher orthostatic increase in plasma norepinephrine (0.8±0.3 nmol/L; 95% CI, 0.2 to 1.3; P=0.01), and caused a 33% increase in urine norepinephrine (5.1±1.1 nmol/L creatinine per day; 95% CI, 2.7 to 7.4, P=0.001), and an 81% increase in urine epinephrine (1.3±0.2 nmol/L creatinine per day; 95% CI, 1 to 2; P<0.001). The peroneal microneurographic sympathetic activity was attenuated by modafinil during orthostatic tilt (P<0.001). α1-Adrenoreceptor function was maintained. Modafinil substantially perturbs autonomic cardiovascular regulation by increase in heart rate and blood pressure. Autonomic changes of this magnitude encourage caution in use of modafinil in patients with cardiovascular disease. (Hypertension. 2005;45:612-618.)

Key Words: blood pressure ■ catecholamines ■ heart rate ■ norepinephrine ■ baroreflex

Modafinil (2-[(diphenylmethyl)sulfinyl]acetamide), a psychostimulant drug used for treatment of daytime sleepiness in narcolepsy,1 is promoted as more potent than caffeine and without the addiction potential of amphetamines. Since Food and Drug Administration approval in 1998 for narcolepsy, use of modafinil has expanded rapidly into the treatment of fatigue, depression, attention deficit hyperactive disorder (ADHD), and sleepiness caused by other medicines. Recently, several athletes tested positive for this drug, and it has been placed on the list of banned stimulants of the United States Olympic Committee.2 The effect of modafinil on the cardiovascular system has attracted attention because analogous drugs such as amphetamine, cocaine, and ephedra alkaloids result in an increased risk of myocardial infarction and extrasystoles.3–5 A drug with psychostimulant effects can potentially alter heart rate (HR) and blood pressure (BP). Some modafinil studies have reported increases in HR and BP6–7 whereas others showed no effect.8–10 Studies evaluating the cognitive enhancing effects,9 abuse potential,11 and anorexigenic effect12 implicate associated involvement of the autonomic nervous system.12 But the effect of modafinil on catecholamines and muscle sympathetic nerve activity (MSNA; microneurography) has not, to our knowledge, been investigated in human subjects. Given the rapidly growing use of modafinil, it is important to define how the drug alters autonomic cardiovascular regulation in healthy subjects. To obtain definitive data on this point, we studied the effect of modafinil on hemodynamic, endocrine, and microneurographic function in normal volunteers.

Methods

General
Studies were conducted at the Vanderbilt University General Clinical Research Center. The local institutional review board approved the experimental protocol. The manufacturer of modafinil provided no support for this study.

Subjects
Subjects were recruited from the Vanderbilt University General Clinical Research Center volunteer database and included in the study after a review of medical history and a comprehensive physical examination to ensure a healthy status. They were compensated for participation. Subjects abstained from all drugs, including caffeine and nicotine, for at least 72 hour before testing. Consenting healthy adult subjects (n=12; 10 males [8 white, 1 Hispanic, and 1 black] and 2 females [1 white and 1 Hispanic] 20 to 46 years of age participated in the study. Race/ethnicity was noted by the investigator as defined by the participants. Their body mass index was 27±1.3 kg/m², resting HR was 61±2 bpm1, and BP was 111±2/65±2 mm Hg. Subjects were studied as inpatients in a randomized, double-blind, cross-over design protocol. Because dietary sodium content modulates autonomic function through plasma renin activity and catecholamines, subjects were

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brought into sodium balance before the first trial and were continued through the second trial. Subjects ingested 400 mg of modafinil or placebo orally for 3 days each. Because the peak of absorption of modafinil is 2 to 4 hours after drug intake in healthy volunteers,13 subjects were tested 2 hours after oral ingestion of modafinil or placebo for 2 days in each phase. Time-of-day of testing was controlled within 1 hour for each subject. The enantiomers of modafinil exhibit linear kinetics on multiple dosing of 200 to 600 mg once daily in healthy volunteers.14 Therefore, we chose a moderate dose of 400 mg (≈3.5 mg/kg) to study the effects on normal volunteers. Washout period between drug conditions was 4 days (96 hours). Given that the half life of modafinil is 12 to 15 hours, this washout period (>5 half lives) should have minimized any risk of carryover effects.

An antecubital intravenous line was placed for blood sampling. All subjects were studied during supine rest beginning at 8:00 AM. Respiration (1132 pneumotrace II; UFI) and HR (ECG; Gould) were measured continuously. Beat-to-beat BP (Finapres; Ohmeda) and brachial BP (Dinamap; Critikon) were determined. An arm sling supported the arm and held the finger on which BP was measured at heart level during tilt. BPs from the automatic system (Finapres) were verified by arm-cuff sphygmomanometry on the contralateral arm.

Subjects underwent an autonomic evaluation that included orthostatic vital signs at rest (supine), during standing, and during graded head-up tilt to 60° on a different day. Standing time (range 0 to 30 minutes) was calculated as the mean time the subjects could stand before the presyncopal symptoms appeared or the tilt study completed.

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Responses to Valsalva maneuver, hyperventilation, hand-grip test, cold pressor test, HR variability, and BP variability were calculated in the time and frequency domain as described previously.15,16 Resting BP and HR were monitored during the 3 days of placebo and modafinil. MSNA and pharmacological baroreflex testing evaluated the efferent and afferent autonomic control.

Venous plasma catecholamine concentrations8,17 were obtained after overnight rest in the supine position and again after 30 minutes in the upright position. They were repeated the following day with graded head-up tilt after overnight rest in the supine position and again after tilt at 60°. Urine was collected from 9 AM 1 day to 9 AM the following inpatient day in the placebo and modafinil phases to determine 24-hour urine volume, sodium, potassium, and creatinine as described.8 Urine and plasma catecholamines were run using the method of Holmes et al18 with variations. Samples were extracted with alumina, and 3,4-dihydroxybenzylamine was added as an internal standard. Eluate was run on a high-performance liquid chromatography consisting of an ESA 542 Autosampler, ESA pump, Axi-chrom column (Thompson Instruments), ESA5011 analytical cell, and Coulouchem II detector.

**Head-Up Tilt**

A restraining strap across the upper abdomen of the subjects secured them to the tilt table during upright tilt. The tilt table rotated around an axis located ~0.5 m behind the thighs of subjects. Subjects were allowed to remain relaxed and quiet throughout all studies and were monitored for any signs of presyncope during all tests.19 After 15 minutes of supine rest, a graded head-up tilt test was performed. The tilt angle was increased by 15° every 5 minutes until an angle of 60° was reached. Plasma catecholamines were obtained in the supine position and after 5 minutes of 60° tilt.

**Autonomic Function Tests**

HR and BP response to controlled breathing, hyperventilation, Valsalva maneuver, hand-grip test, and cold pressor test20 were assessed. Respiratory sinus arrhythmia was calculated as the coefficient between the longest and shortest R-R intervals during 8 respiratory cycles. The Valsalva ratio was calculated as the coefficient between the longest R-R interval during phase IV and the shortest R-R interval during phase II of the Valsalva maneuver. For isometric hand-grip testing, participants squeezed a hand-grip dynamometer at 30% of maximal voluntary contraction over 3 minutes. The cold pressor test was performed by ice water immersion of the right hand for 1 minute.

**HR and BP Variability**

HR variability and BP variability were calculated in the time and frequency domain. Fast Fourier transformation was used for spectral analysis (window 256 s; resolution 0.004 Hz; after subtraction of the mean, trend removal, spline interpolation, and resampling with 4 Hz). High-frequency power (0.15 to 0.4 Hz) and low-frequency power (0.04 to 0.15 Hz) were calculated as mean values over the frequency band.16

**Pharmacological Testing**

Pharmacological testing was performed with subjects in the supine position as described previously.19 After reaching a stable baseline, incremental boluses (0.1 to 1.6 μg/kg) of sodium nitroprusside (NTP) and phenylephrine (PHE; 12.5 to 400 μg) were given to depress or raise BP by 25 mm Hg to determine pharmacological baroreflex curves. Incremental bolus doses of PHE and NTP were administered into a large antecubital vein. HR and BP changes were determined as described previously.

**Microneurography**

MSNA was recorded from the peroneal nerve.21 Recording was done randomly in either of the legs, once each for modafinil and placebo phase. A unipolar tungsten electrode ( uninsulated tip diameter 1 to 5 μm, shaft diameter 200 μm; Frederick Haer and Co.) was inserted into the muscle nerve fascicles of the peroneal nerve at the fibular head for multi-U recordings. Nerve activity was amplified with a total gain of 100 000, band pass filtered (0.7 to 2 kHz), and integrated (Biomedical Engineering Department; University of Iowa, Iowa City). Criteria for adequate MSNA recording included: (1) pulse synchrony; (2) facilitation during Valsalva strain and suppression during the hypertensive overshoot after release; (3) increases in response to breath-holding; and (4) insensitivity to startle (ie, loud noise).21,22 MSNA was expressed as burst rate (bursts/min).

**Data Acquisition**

Data were collected in a quiet room at a constant temperature of 20°C to 21°C and analyzed by a single investigator blinded to experimental randomization of drug. Physiological signals were digitized online during placebo and modafinil phases with Windaq hardware and software (DA-220; Datica Instruments). R-R intervals, diastolic BP, systolic BP values, and respiration were defined off-line for the complete records using a custom-written software in PV-Wave (PV-Wave; Visual Numerics, Inc.). Baroreflex slopes were calculated as described previously.16 Sympathetic bursts were identified by a computer algorithm and then were confirmed by the investigator who was blinded to the experimental context. Bursts were selected if the signal-to-noise ratio was >2:1, and bursts occurred ~1.3 s after the previous (1 removed) electrocardiographic R wave. The number of bursts per minute (burst rate) was used as a quantitative index. HR, arterial pressure, and MSNA were averaged for 1 minute of baseline.

**Statistical Analysis**

It was estimated that a sample size of 8 will have 81% power to detect an effect size of 1.0 using a paired t test with a 0.05 1-sided significance level, where the effect size is the difference between the means divided by the SD of the difference. To ensure adequate numbers of subjects completing both phases of the study, the number of subjects was later increased to 12. All analyses were conducted using the SPSS for Windows version 11 statistical package (SPSS). Values of each of the above variables from individual subjects were averaged for each group and expressed as mean ± SEM. This procedure was also followed for the changes in different tests for BP, MSNA, HR, and catecholamines induced by placebo and modafinil. Difference between the group means for continuous measurements
was tested by paired t-test and checked by Mann–Whitney U test. A general linear model repeated-measure ANOVA was used to assess changes from baseline while assessing group differences between the 2 treatment phases (placebo and modafinil). A value of \( P < 0.05 \) was considered statistically significant. We report the absolute P values as 2-tailed without correction for multiple comparisons.

**Results**

**Cardiovascular Parameters**

The resting HR and resting BP increased significantly 2 hours after the modafinil when a mean increment of resting HR, \( 9.2 \pm 2.0 \) bpm (95% confidence interval [CI], 4.7 to 13.6; \( P = 0.001 \)), resting systolic BP, \( 7.3 \pm 3.2 \) mm Hg (95% CI, 0.2 to 14.4; \( P = 0.044 \)), and resting diastolic BP by \( 5.3 \pm 1.7 \) mm Hg (95% CI, 1.4 to 9.1; \( P = 0.012 \)) was observed (Figure 1). Of the 12 subjects, 3 felt dizzy in the modafinil phase only and did not complete the posture test. The standing time (posture test) was similar in both phases (30.0 ± 2.2 versus 26.4 ± 2.4 minutes; \( P = 0.167 \)). Of 12 subjects, 2 felt presyncopal in both phases, 2 in modafinil phase, and 2 in placebo phase. Tolerance to tilt (in minutes) was similar in the 2 regimes (18.1 ± 0.9 versus 17.9 ± 0.9; \( P = 0.853 \)). Modafinil increased HR and systolic BP significantly in response to orthostatic tilt (Figure 2; \( P = 0.001 \)). Modafinil decreased resting HR variability high frequency (v) and increased resting HR variability low frequency (r, Table 1). Baroreflex sensitivity, HR variability in response to tilt and
pharmacological stressors (PHE and NTP), and autonomic function tests (controlled breathing, hyperventilation, Valsalva maneuver, hand-grip test, and cold pressor test) were similar between placebo and modafinil phase (Table 1).

**Plasma and Urine Catecholamines**

Modafinil elicited increases in 24-hour urinary norepinephrine (NE) and Epi (Figure 3; \(P=0.001\)), plasma NE, dihydroxyphenylglycol (DHPG), dihydroxyphenylalanine (dopa), and dihydroxyphenyl-acetic acid (DOPAC) in response to orthostatic change in posture (Table 2; \(P<0.05\)). The DHPG/NE ratio was similar in subjects with placebo and modafinil. The microneurographic burst activity and HR increased for placebo and modafinil. When comparing the 2, the burst activity per minute with modafinil was suppressed continuously than with placebo (Figure 4; \(P=0.012\)). The microneurographic burst activity and HR increased (decreased R-R interval) in both the phases in placebo and modafinil, with increasing degrees of tilt, but modafinil elicited lower burst activity and higher HR (lesser R-R interval) when compared with placebo for the same degrees of tilt.

**Urine Volume and Urinary Electrolytes**

Urine volumes and electrolytes were similar in placebo and modafinil phases. Modafinil had no effect on creatinine excretion. There were no significant correlations between maximal changes in plasma epinephrine (Epi) and HR \((r=0.14; P=0.665)\), systolic BP \((r=0.04; P=0.910)\), or diastolic BP \((r=0.35; P=0.261)\).

**Discussion**

The most important new information from our study is that modafinil elicits significant elevation in BP and HR, together with sustained adrenomedullary activation. These effects have been underestimated in the literature. Studies that conclude that use of modafinil in clinical conditions has minimal or absent autonomic cardiovascular activation\(^{23-26}\) were generally not undertaken under optimal control conditions (abstinence of concurrent drugs, caffeine, alcohol, and nicotine, strict dietary sodium and potassium balance, and hospitalization to ensure control of food intake and physical activity).
There was no change in urinary sodium or potassium excretion, indicating that the BP increase was not attributable to retention of sodium with expansion of extracellular fluid. Likewise, urinary electrolytes rule out any mechanism involving increase in mineralocorticoid as a basis for the pressor action.

In addition to the rise in HR and systolic BP, the decrease in high frequency and the trend toward an increase in the low-frequency component of HR variability, modafinil increased plasma NE, dopa, DOPAC, and DHPG levels. There was a parallel rise in urinary NE and Epi in response to orthostatic change. The relative changes of Epi were greater than changes in NE (almost double), although the arterial Epi concentration was likely much higher than the venous levels because of extraction of Epi during passage of blood through the forearm tissues. A total of 33% of normal volunteers had presyncopal symptoms and were not able to complete the tilt test. The stress of presyncope can also lead to higher Epi levels, but a presyncopal episode is too short to account for the substantial elevation in the 24-hour urinary Epi we observed. Because the number of subjects presyncopal in the 2 phases of the study were not significantly different, the overall increase of Epi in the modafinil phase compared with the placebo phase assumes greater significance. The ratio of Epi/NE after modafinil is higher than after sympathetic stimuli such as sodium restriction and upright posture and qualitatively resembles the smaller adrenomedullary discharge observed after large oral doses of caffeine in noncaffeine-using normal volunteers or as seen with insulin hypoglycemia. This increased Epi might be indirectly stimulating NE release from neuron terminals via β-adrenoceptors.

Dopa is the product of tyrosine hydroxylase, the rate-limiting step in NE synthesis. The increase in levels of dopa and its metabolite DOPAC suggest that there is increased activity of tyrosine hydroxylase, either because of sympathetic activation or an allosteric enhancement of activity of the enzyme. For example, quite high levels of dopa and DOPAC are seen in dopamine-beta-hydroxylase deficiency, presumably because of excessive drive of tyrosine hydroxylase in the absence of physiological allosteric hindrance by NE. With prolongation of a sympathetic stimulus, higher levels of these sometimes track with sympathetic activation. The similar DHPG/NE ratio after placebo and modafinil suggests that NE from the vesicle could drive DHPG higher, obscuring a small effect of NET blockade. Further in vitro studies are required to fully assess potential involvement of NET.

Microneurography is sometimes considered a peripheral display of central sympathetic activity. With increases in plasma NE, Epi, dopa, DOPAC, urinary NE and Epi, resting HR, and BP, an increase in microneurography bursts might have been expected. However, differential sympathetic activation in various tissue beds is encountered increasingly. This presumably accounts for the decreased microneurography burst activity despite concomitant rise in catecholamines by modafinil. However, clearly, there was selectively increased

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<th>TABLE 2. Effect of Modafinil on Plasma and Urine Catecholamines</th>
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<td>Urinary (24 hours)</td>
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<td>Epi, nmol/L creatinine, mmol/L</td>
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<td>Dopamine, nmol/L creatinine, mmol/L</td>
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Values are means ± SEM.
Upright indicates after 30 minutes at standing in orthostatic posture test; Δ, difference in values from supine to upright.
*P<0.05; †P<0.01; ‡P<0.001 (significant differences between the groups).

Plasma catecholamines were expressed as nmol/L. Urinary catecholamines were standardized as nmol/L creatinine.
cardiac adrenoceptor stimulation. It could be possible that modafinil had a direct or indirect peripheral effect that contributed to the pressor response and that the MSNA response was attributable to a reflex effect, as shown in earlier studies with cocaine.30 Such a constellation of tachycardia, hypertension, and decreased MSNA occurs also in the fight or flight response,31,32 after tyramine infusion,33 tachycardia, hypertension, and decreased MSNA occurs also in the fight or flight response,31,32 after tyramine infusion,33 and in pheochromocytoma patients.34 It has been observed that in sleep apnea, which is associated with higher sympathetic tone; modafinil did not elevate the resting sympathetic tone further, although sympathetic effect on mental and physical load could be shown.10 Unlike modafinil, other psychostimulants such as amphetamine elevated plasma NE, systolic and diastolic BP, but not HR or plasma Epi.35 Caffeine increased plasma NE, Epi, and systolic and diastolic BP, but HR increases after a brief decline;3 methylphenidate increased Epi, systolic BP, and diastolic BP, but not plasma NE.36 This indicates that modafinil, at least in part, may engage distinct central mechanisms.

In conclusion, modafinil causes a strong central adrenergic response, as indicated by increased levels of catecholamines (plasma NE, dopa, DOPAC, urinary NE, and Epi), HR, and BP. This is attributable in part to adenomедullary discharge, as evidenced by increased Epi excretion. We attempted to study an equal number of males and females, but because of non-study-related (personal) circumstances, 10 males and only 2 females completed the study. Because of potential differences in many measures under investigation, it would be wise to conduct a study with an equal number of men and women. Although this is a cross-over design in which each subject acted as his/her own control, interpretation is limited by its small sample size, which permits detection of only large effects; some effects of interventions could be missed, and effects reported here might therefore be considered large amplitude. A long-term influence on BP cannot be extrapolated from a single-dose treatment. Studies of the long-term treatment of patients with concomitant cardiovascular diseases (eg, hypertension) with modafinil should include measurement of cardiovascular parameters. Such a study is desirable to evaluate modafinil compared with substances such as caffeine or amphetamines, which are known to have profound effects on the cardiovascular system.

**Perspectives**

Adrenergic activation caused by modafinil could increase the number of individuals with elevated BP. This encourages caution in use of modafinil in patients with cardiovascular disease or those engaging in strenuous physical activity. In light of these studies, careful monitoring of individuals receiving modafinil for possible cardiovascular complications seems prudent.

**Acknowledgments**

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