Effect of Modafinil on Autonomic Cardiovascular Function during Isometric Hand Grip Strength Test

Sinha B*

Abstract

Background: Modafinil, a centrally acting alpha-adrenergic agonist, promoting wakefulness, has been approved for use by the Armed Forces Personnel across the world for sustained duration operation.

Methods: The effect of single dose (200 mg) of Modafinil on autonomic cardiovascular reactivity during Isometric Hand Grip (IHG) strength test at 30% of maximal contraction intensity was examined in 11 healthy Indian males. Another group of 11 healthy Indian males serving as control group were administered placebo. The study was a double blinded, placebo controlled and randomized trial. Heart Rate (HR) and Blood Pressure (BP) were recorded at resting baseline and during IHG test, before and after 4 h of administration of the drug/ placebo.

Results: HR increased significantly in the Modafinil group as compared to the placebo group (97.3±8.08 bpm and 84.4±8.69 bpm; $p<0.01$) during IHG. The systolic and mean arterial pressure increased during IHG in the Modafinil group as compared to placebo group.

Conclusion: An increase in autonomic cardiovascular reactivity to IHG test was observed in individuals taking Modafinil as compared to placebo.

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Keywords: Modafinil, Autonomic cardiovascular function, Isometric hand grip test, Heart rate, Blood pressure.

Introduction

Modafinil is a centrally acting alpha-adrenergic agonist and promotes wakefulness. This drug is used for the treatment of Narcolepsy, shift work sleep disorders and excessive daytime sleepiness [1-2]. Modafinil is a relatively new alertness-enhancing compound of interest to the military aviation community [3]. Modafinil may substantially perturb autonomic cardiovascular function as reported in the scientific literature [4]. Modafinil presumably exerts its action on the central adrenergic system thus causing an increase in arousal level. It is likely that Modafinil administration will also cause an activation of sympathetic neural system. Increased sympathetic tone leading to systemic side effects with Modafinil use has been reported in the literature [5]. The effect of Modafinil administration on autonomic cardiovascular reactivity during Isometric handgrip strength (IHG) test has not been studied much. An earlier scientific study by Taneja et al examined the effect of administration of 400 mg of Modafinil on autonomic cardiovascular reactivity during cold pressor test, head-up tilt test and IHG test [4]. Indian Air Force (IAF) has permitted the use of Modafinil to Pilot for extended duration wakefulness beyond 16 h and the dosage for Modafinil has been recommended to be 200 mg daily.

Isometric Handgrip (IHG) exercise is an autonomic neural function challenging task which lead to increase in the sympathetic outflow and decrease in parasympathetic activity. During IHG exercise, an increase in the blood pressure response was observed [6]. No study has examined the effect of administration of single dose of 200 mg of Modafinil on autonomic cardiovascular

**Scientist 'E', Ph D Physiology, Professor and Head, Dept of Space & Environmental Physiology, IAM, IAF*

reactivity during IHG test. The effect of administration of Modafinil on autonomic cardiovascular reactivity during IHG test may be additive due to its ability to exert action on the sympathetic neural activity. The present study examined the effect of administration of Modafinil on autonomic cardiovascular functions during isometric hand grip test in a group of healthy Indian males in a randomized, double-blinded, placebo controlled trial.

Material and methods

22 healthy male volunteers were selected for the present study. The participants were non-smokers and occasional drinkers. The participants were instructed to refrain from consuming alcohol and tobacco 48 hours before the study. They were also instructed not to consume any tea or coffee 4 hours before the baseline recording and up to 6 hours after intake of placebo or Modafinil. Participants with any cardiovascular and autonomic co-morbidity were excluded from the study. The participants were randomly divided into two equal groups consisting of 11 volunteers in each group. One group was designated as 'Placebo' group and the other group as 'Modafinil' group. The participants were explained in detail about the possible consequences of intake of Modafinil. The study protocol was approved by the Ethics committee of the Institute of Aerospace Medicine, Bangalore. Voluntary informed consent was taken from each participant for taking part in the study.

Each participant reported to the laboratory at 0800 hours in the morning. Their baseline HR and BP were recorded in the sitting position. The participant was then instructed to perform isometric handgrip test with their dominant hand. They carried out the test in sitting position with elbow flexed at 90° by a calibrated handgrip dynamometer. The maximal isometric force generated by the dominant hand during maximal voluntary contraction (MVC) test was recorded three times 1-2 minutes apart. The average of the maximal force of three trials was computed for each volunteer. After a sufficient rest period, the volunteer was then asked to maintain isometric contraction intensity in the handgrip dynamometer at 30% of MVC for 4 min. The investigator encouraged the volunteer to maintain the work intensity throughout the trial. After recording baseline physiological parameters during the test, the participant was given a single dose of either placebo or 200 mg of Modafinil orally in random order. The post-drug IHG test was carried out after four hours of either placebo or Modafinil administration. The four hour time gap was given between baseline and post-drug trial as Modafinil takes about four hours to reach its peak concentration in the plasma [7]. The volunteers maintained the contraction intensity at 30% of MVC during post-drug trial. The physiological parameters were recorded during the test after administration of the drug.

The HR was recorded by single lead electrocardiography (Lead II) by a physiological data recorder Procomp Infiniti 5.0 (Thought Technology, Montreal, Canada). Three electrodes were placed on the anterior surface of the skin on the chest, one just below the right shoulder; another just below the left shoulder and a third electrode near the umbilicus.

Non-invasive arterial blood pressure was recorded on a beat to beat basis by Arterial Tonometer (Finometer, Finapres Medical System, Amsterdam, Netherlands). For recording beat by beat blood pressure, a finger cuff was attached around middle phalanx of the middle finger in the non-dominant hand. This method of recording continuous blood pressure is based on the volume-clamp technique discovered by the Czech physiologist Jan Peòáz [8-9]. The Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Mean Arterial Pressure (MAP) and Pulse Pressure (PP) were recorded and expressed in mm Hg.

Other parameters like Stroke Volume (SV in ml/beat) Cardiac Output (CO in L/min), Aortic Impedance (AI in medical unit as mMU) and Arterial Compliance (AC in medical unit as MU) were calculated by the software of the arterial tonometer.

The professional statistical software Statistica 6.0 was used to analyse the data. The data was first checked for normality by Shapiro Wilks 'W' statistic. Unpaired t-test

was carried out for intergroup comparison. Two factors repeated measure ANOVA was carried out for testing the effect of Modafinil on physiological responses i.e. HR and BP. The first factor was type of medication administered, which had two levels 'Placebo' and 'Modafinil' and second factor was time of testing, which again had two levels 'before administration of drug/ placebo' and 'after administration of drug/ placebo'. After significant outcome from ANOVA, post-hoc analysis was carried out by Tukey's HSD test for individual comparison. The level of significance was kept at $p<0.05$ and considered to be as significant.

Results

Table 1 shows physical characteristics of the volunteers. Modafinil group had a significantly higher body height than placebo group.

Table 1 – Characteristics of the participants

Parameters	Placebo Group Mean ± SD	Modafinil Group Mean ± SD	Level of significance ^ (p value)
Age (years)	25.5±5.07	22.9±1.37	NS
Body height (cm)	173.1±4.70	177.5±3.69	S*
Body weight (kg)	68.1±10.59	72.4±7.47	NS

NS: Not Significant; * significant at p=0.025

Table 2 shows cardiovascular responses during IHG test in placebo and Modafinil group before and after administration of placebo and Modafinil. The results of HR, SBP, DBP, MAP, PP, SV, CO, AI and AC are shown in the Table.

Table 2- Cardiovascular Parameters at baseline and during IHG in Placebo (n=11) and Modafinil (n=11) treated group before and after administration of the drugs. Values are in mean ± SD.

Parameters	Placebo Group				Modafinil Group			
	Before		After		Before		After	
	Base-line	IHG	Base-line	IHG	Base-line	IHG	Base-line	IHG
HR (bpm)	76.0± 9.62	78.8± 10.02	81.6± 8.06 **	84.4± 8.69 **$$**	77.5± 9.50	83.9± 6.23 ***	91.5± 10.54 ***b	97.3± 8.08 +++ **$$$ d**
SBP (mm Hg)	122.4± 9.64	137.3± 11.60***	127.5± 8.94	139.1± 13.25 +++	125.8± 10.11	142.0± 11.84 *	145.9± 20.8**b	151.2± 8.47**c**
DBP (mm Hg)	80.4± 8.63	90.6± 10.73***	82.8± 9.51	90.9± 12.63 ++	82.6± 7.29	93.2± 7.53 ***	92.0± 5.62 *** **b**	99.3± 4.35 +++ $$$
MAP (mm Hg)	96.4± 8.31	109.7± 11.64***	99.6± 9.24	109.7± 12.93 ++	98.9± 7.85	112.6± 9.26 ***	109.8± 6.39 *** **b**	119.4± 5.8+++ **$$$ c**
PP (mm Hg)	42.0± 5.40	46.7± 4.69***	44.7± 6.03 **	48.2± 5.05 +++	43.2± 5.77	48.8± 6.42 ***	47.9± 7.39 ***	51.8± 7.21++ **$**
SV (ml/beat)	67.0± 13.66	69.3± 17.06	68.6± 14.49	68.1± 14.33	73.5± 11.14	75.0± 11.57	66.6± 9.41 ***	67.4± 9.73**$$$**
CO (L/min)	5.1± 1.48	5.5± 1.81	5.6± 1.23	5.7± 1.35	5.7± 1.02	6.3± 1.19 ***	6.0± 1.07 **	6.5± 1.21 +++
AI (mMU)	51.8± 3.48	54.0± 4.73 **	52.1± 2.52	54.1± 3.66 +	49.3± 3.32	51.5± 3.97 ***	51.1± 3.84 ***	53.0± 3.82 **+++$$$**
AC(MU)	2.29± 0.29	2.03± 0.38 ***	2.23± 0.27	2.00± 0.33 ++	2.54± 0.29	2.16± 0.30 ***	2.20± 0.28***	1.97± 0.24++ **$$**

HR- heart rate (beats per minute); SBP- systolic blood pressure (mm Hg); DBP- diastolic blood pressure (mm Hg); MAP- mean arterial pressure (mm Hg); PP- pulse pressure (mm Hg); SV- stroke volume (ml/beat); CO- cardiac output (L/min); AI- aortic impedance (mMU- medical Unit); AC- arterial compliance (MU- medical unit).

IHG - Isometric Hand Grip Test

Results of repeated measure ANOVA: * compared to pre-drug baseline; + compared to post-drug baseline; $ comparison between pre-drug IHG and post-drug IHG;

*/**/*** $p<0.05$, $p<0.01$ and $p<0.001$

+/++/+++ $p<0.05$, $p<0.01$ and $p<0.001$

$/$$/$$$ $p<0.05$, $p<0.01$ and $p<0.001$

Results of Un-paired t-test: a: $p<0.05$-Placebo vs. Modafinil (before drug); b: $p<0.01$ (before drug); c: $p<0.05$ (after drug); d: $p<0.01$ (after drug).

Heart Rate (HR)

HR increased significantly during IHG in placebo group after its administration by about 7% as compared to without placebo (78.8 vs. 84.4 bpm; $p<0.01$) (Table 2). The HR increased by about 16% during IHG after administration of Modafinil as compared to IHG performed without Modafinil (83.9 vs. 97.3 bpm; $p<0.001$). HR when compared between two groups during IHG revealed that Modafinil group had a significantly higher HR as compared to placebo (97.3 vs. 84.4 bpm; $p<0.01$).

Systolic Blood Pressure (SBP)

The SBP did not increase during IHG when compared between pre-placebo and post-placebo (137.3 and 139.1 mm Hg). Similar was the case with Modafinil group (142.0 and 151.2 mm Hg). However, SBP was significantly higher during IHG after Modafinil administration as compared to placebo (151.2 vs. 139.1 mm Hg; $p<0.05$).

Diastolic Blood Pressure (DBP)

DBP increased significantly from baseline to IHG before (80.4 to 90.6; $p<0.001$) and after (82.8 vs. 90.9 mm Hg; $p<0.01$) placebo administration. DBP did not differ significantly during IHG between pre-placebo and post-placebo (90.6 and 90.9 mm Hg). DBP also increased significantly in Modafinil group from baseline to IHG before (82.6 vs. 93.2 mm Hg; $P<0.001$) and after (92.0 vs. 99.3 mm Hg; $p<0.001$) its administration. Baseline DBP increased after administration of Modafinil (82.6 to 92.0 mm Hg; $P<0.001$). DBP increased significantly during IHG when compared between pre-Modafinil and post-Modafinil (93.2 vs. 99.3 mm Hg; $p<0.001$).

Mean Arterial Pressure (MAP)

MAP increased significantly during IHG from baseline before administration of placebo (96.4 to 109.7 mm Hg; $p<0.001$) and Modafinil (98.9 to 112.6 mm Hg; $p<0.001$). Post administration, MAP increased significantly during IHG from baseline in placebo treated group (99.6 to 109.7 mm Hg; $p<0.01$) and in Modafinil treated group (109.8 to 119.4 mm Hg; $p<0.001$). MAP did not differ significantly during IHG between pre-placebo and post-placebo (109.7 and 109.7 mm Hg), but in Modafinil group, the MAP was significantly higher between pre-Modafinil and post-Modafinil (112.6 and 119.4 mm Hg; $p<0.001$).

MAP increased significantly at baseline after Modafinil administration (98.9 to 109.8 mm Hg; $P<0.001$) and an increase in MAP during IHG (112.6 to 119.4 mm Hg; $p<0.001$) from pre-Modafinil IHG. Unpaired t-test showed that MAP was significantly higher during IHG in Modafinil group than placebo group (119.4 vs. 109.7 mm Hg; $p<0.05$).

Pulse Pressure (PP)

PP increased significantly during IHG from baseline before administration of placebo (42.0 to 46.7 mm Hg; $p<0.001$) and Modafinil (43.2 to 48.8 mm Hg; $p<0.001$). Post administration, PP increased during IHG from baseline in placebo group (44.7 to 48.2 mm Hg;

p<0.001) as well as in Modafinil group (47.9 to 51.8 mm Hg; p<0.01). PP was significantly higher during IHG when compared between pre-Modafinil and post-Modafinil (48.8 vs. 51.8 mm Hg; p<0.05), but this increment in PP was not observed in placebo group (46.7 vs. 48.2 mm Hg).

Stroke Volume (SV)

SV remained unaltered in placebo and Modafinil group during IHG except a decrement in baseline SV was observed in Modafinil group (73.5 to 66.6 ml/beat; p<0.001) and also during IHG as compared to pre-Modafinil IHG (75.0 vs. 67.4 ml/beat; p<0.001).

Cardiac Output (CO)

CO increased during IHG from baseline before (5.7 to 6.3 L/min; p<0.001) and after administration (6.0 to 6.5 L/min; p<0.001) of Modafinil. There was an increment in baseline CO after Modafinil administration (5.7 to 6.0 L/min; p<0.01). No statistically significant changes were observed in the placebo group.

Aortic Impedance (AI)

AI increased during IHG before placebo (51.8 vs. 54.0 mMU; p<0.01) and after placebo (52.1 vs. 54.1 mMU; p<0.05). AI also increased during IHG before (49.3 vs. 51.5 mMU; p<0.001) and after (51.1 vs. 53.0 mMU; p<0.001) administration of Modafinil. A significant increase in baseline AI was observed in Modafinil group (49.3 to 51.1 mMU; p<0.001). When compared between pre-Modafinil and post-Modafinil IHG, AI increased significantly after Modafinil administration (51.5 to 53.0 mMU; p<0.001).

Arterial Compliance (AC)

AC decreased during IHG from pre-placebo baseline (2.29 vs. 2.03 MU; p<0.001) and post-placebo baseline (2.23 vs. 2.00 MU; p<0.01). AC also decreased during IHG from baseline before Modafinil administration (2.54 vs. 2.16 MU; p<0.001) and from baseline after Modafinil administration (2.20 vs. 1.97 MU; p<0.01). A significant decrease in baseline AC was observed in Modafinil group (2.54 vs. 2.20 MU; p<0.001).

Discussion

The present study examined the effects of Modafinil on autonomic cardiovascular function in a group of healthy Indian males during isometric handgrip test. The effect of Modafinil on cardiovascular system has attracted attention recently as other analogous wake-promoting agents like Amphetamine and Cocaine result in an increased risk of myocardial infarction and extrasystoles [10-12]. Modafinil is a new alertness-enhancing compound of interest to the military aviation community. The main finding of the present study was that Modafinil caused a sustained elevation in heart rate and blood pressure in participants during isometric handgrip exercise when compared with heart rate and blood pressure of individuals taking placebo. The comparatively higher heart rate and blood pressure were even noticed at baseline in the participants taking Modafinil. Intergroup comparison revealed that HR, SBP, DBP and MAP were not different between placebo and Modafinil group at baseline and during IHG before administration of either placebo or Modafinil. Post-Modafinil, the baseline heart rate increased by 18% (P<0.05), SBP by 16% (P<0.01), DBP by 11% (P<0.01), and MAP by 11% (P<0.01) as compared to the placebo group who showed an increase in HR, SBP, DBP, and MAP by 7%, 4%, 3% and 3% respectively. Taneja et al reported that administration of 400 mg of Modafinil increases resting heart rate by 9 bpm (p<0.001) [4]. Kpaeyeh et al reported that oral intake of 100 mg of Modafinil did not have any impact on orthostatic HR for 4 hours of standing when compared with placebo but SBP was significantly raised either in seated or supine condition [13]. Heart rate when compared between handgrip tests with and without Modafinil, it was observed that Modafinil intake increased HR significantly (84 to 97 bpm, 16%). The HR increase observed after placebo administration was much lesser (78.8 to 84.4, 7%). SBP, DBP and MAP increased by about 6% during handgrip test after Modafinil intake as compared to handgrip test performed without Modafinil. SBP, DBP and MAP during handgrip did not

change between pre and post placebo administration. This clearly indicates that Modafinil exaggerates the autonomic cardiovascular response during handgrip test. Northcote et al reported an increase in HR by 15% and SBP by 27% during sustained isometric handgrip exercise at 30% of maximal contraction intensity in healthy males [14]. An increase in SBP by 45% and DBP by 31% during isometric handgrip has also been reported in the literature [15].

The precise mechanism of action of Modafinil is unclear. It has been suggested that Modafinil binds directly with Dopamine and Norepinephrine transporter in the brain and may exert a significant inhibition of both catecholamine transporters [16-17] leading to significant elevation of Dopamine, Norepinephrine, 5-Hydroxytryptophan, Glutamate, Histamine level and reduction in Gamma Amino Butyric Acid. It has been reported that Modafinil is an exceptionally weak but very selective Dopamine transporter inhibitor [18]. Positron emission tomography imaging study has confirmed that administration of single dose of 200 mg of Modafinil in human causes 51% of Dopamine transporter occupancy [19].

The Isometric handgrip test is a form of sustained voluntary isometric contraction of the upper limb muscles. The isometric contraction of the muscle rapidly induces an increase in heart rate and blood pressure. Research has reported that the increase in heart rate during sustained isometric handgrip test occurs due to the withdrawal of parasympathetic neural activity rather than an increase in sympathetic activity [20]. This was confirmed by the researchers who observed that no increase in heart rate was observed after administering parasympathetic blockade like Atropine during IHG [20]. The role of sympathetic neural drive during IHG was observed to mediate their action after 10 seconds of the test [21].

Isometric exercise is characterized by the build-up of metabolites in the contracting muscle, which are not removed easily due to sustained contraction of the muscle causing occlusion of blood flow through them. Metabolites, in turn, activate 'Type IV afferent nerve endings' in the muscle, known as 'metabolic receptor' or 'muscle metaboreceptor'. Mechanical changes in muscles and tendons during isometric contraction can also activate 'Type III afferent nerve endings' in the muscles known as 'mechanoreceptor'. Muscle metaboreflex and mechanoreflex together constitute the exercise pressor reflex that becomes sensitized to the mechanical and metabolic conditions of the contracting muscles and send the information to the medullary cardiovascular center. The cardiovascular center accordingly adjusts the sympathetic and vagal tone taking into account the metabolic and mechanical status of the contracting muscles [22]. The typical consequence of metaboreflex recruitment is an increase in MAP [23]. The comparatively higher MAP in Modafinil group might clarify the role of Modafinil in causing a heightened sympathetic response during isometric handgrip test.

The stroke volume decreased at baseline after Modafinil administration (73.5 to 66.6 ml/beat; $p<0.001$) and during IHG (75.0 to 67.4 ml/beat; $p<0.001$). This kind of reduction in SV was not observed in individuals taking placebo where it remained almost similar during handgrip test as compared to baseline both before and after its intake. However, the comparatively higher increases in HR after Modafinil intake has helped the participants to achieve a comparatively higher cardiac output in Modafinil group than their placebo treated counterpart.

The Aortic impedance is a measure of the afterload to the heart and is calculated as aortic pressure divided by aortic flow at that instance. The increased aortic impedance reduces aortic compliance thus causing a reduction in stroke volume [24]. The aortic impedance did not differ significantly between pre- and post-placebo handgrip tests. However, it increased significantly during handgrip test after Modafinil intake when compared with its pre-Modafinil value. Modafinil administration caused a reduction in aortic compliance at baseline (2.54 to 2.20 MU; $p<0.001$) and during IHG (2.16 to 1.97 MU; $p<0.01$). The decrease in aortic compliance was associated with an increase in aortic impedance both at baseline (49.3

to 51.1 mMU; P<0.001) and during IHG (51.5 to 53.0 mMU; p<0.001). This decrement in aortic compliance and a corresponding increase in aortic impedance were not observed in placebo group. The increased aortic impedance might have resulted in a reduction in stroke volume in the Modafinil group.

Conclusion

In conclusion, the cardiovascular response during isometric handgrip test after Modafinil administration showed an augmented heart rate and blood pressure response as compared to placebo. Thus, the impact of Modafinil administration on cardiovascular response appeared to be cumulative in causing heightened sympathetic activity which is normally observed during isometric handgrip contraction.

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Conflicts of interests - Nil

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