

Pharmacokinetic Study of Modafinil in Relation to Gender and Ethnicity in Healthy Young Chinese Volunteers

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ABSTRACT- Purpose. Pharmacokinetics of modafinil were investigated in relation to sex and ethnicity in healthy young volunteers from Han, Mongolian, Korean, Uygur and Hui (n = 10/group) following administration of a single 200 mg oral dose. **Methods.** Blood samples were collected over 48 h for the determination of plasma levels of modafinil and its acid metabolite by HPLC. Pharmacokinetic parameters were evaluated using noncompartmental methods. **Results.** Modafinil was well tolerated and safe at a single oral dose of 200 mg. All participants reported adverse events, none of which was serious or unexpected. The maximum plasma concentration (C_{max}) and area under the curve for modafinil concentration versus time, which was extrapolated to infinity ($AUC_{0-\infty}$), were higher in women compared to men ($p < 0.01$). No sex-based difference was noted in the total body weight-normalized modafinil oral clearance. The total body weight-normalized modafinil apparent volume of distribution and $t_{1/2}$ were found to exhibit ethnicity-based significant differences. **Conclusion.** There are pharmacokinetic differences based on sex and ethnicity for modafinil.

INTRODUCTION

Modafinil (\pm -2-[(diphenylmethyl) sulfinyl] acetamide, Figure 1), as a novel wake-promoting psychostimulant discovered by Laboratoier L. Lafon (Maisons Alfort, France), was initially investigated for the treatment of excessive daytime sleepiness (EDS) associated with narcolepsy (1). Recent evidence has indicated that modafinil is effective in the treatment of excessive day-time sleepiness (and fatigue) in disorders other than narcolepsy, such as idiopathic hypersomnia (2), night-shift sleep disorder (3), obstructive sleep apnoea (4), multiple sclerosis (5), Parkinson's disease (6), myotonic dystrophy (7), depression (8), schizophrenia (9), attention-deficit disorder (10), and cocaine dependence and withdrawal (11). The exact mechanism of its wake-promoting activity in the brain is still under investigation, however, it has been reported that it may indirectly increase wakefulness partly through inhibition of gamma aminobutyric acid (GABA) release via serotonergic mechanisms (12). Modafinil has a low abuse potential (13), which produces relatively small changes in cardiovascular activity at clinical doses (14), and does not demonstrate signs of tolerance to its wake-promoting effects even after 12 months of treatment (15). Modafinil is metabolized into two major metabolites, modafinil acid (2-[(diphenylmethyl) sulfinyl] acetic acid) and modafinil sulfone (2-[(diphenylmethyl) sulfanyl] acetamide; Figure 1), which are inactive and the

acid metabolite accounts for more than 60% of the dose (16). The sulfone metabolite is found in minute quantities in plasma so we haven't investigated it in this present study.

Modafinil is well absorbed following oral administration with a terminal half-life of 10 to 15 h, which exhibits linear pharmacokinetics following oral doses ranging from 50 to 400 mg. The oral clearance (CL/F) of modafinil is 50 to 60 mL/min, and the apparent volume of distribution (Vd/F) is 50 to 60 L which indicates the possibility of tissue binding. Its plasma protein binding reaches approximately 60% (17). In addition, the CL/F of modafinil in females is reported to be approximately 22% higher than that in males (16). Pharmacokinetic differences between sexes and ethnic groups have been reported (18-20). Furthermore, sex-specific differences such as menopause, menstruation and the use of contraceptives may influence pharmacokinetics and pharmacodynamics (21). Thus, it is important to investigate possible ethnicity- and sex-based differences in modafinil pharmacokinetics in healthy young Chinese volunteers.

The purpose of the present study was to examine the influence of ethnicity and sex on the pharmacokinetics of modafinil following of a single

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200 mg oral doses of modafinil in Chinese Han, Mongolian, Korean, Uygur and Hui healthy subjects in China. To the best of our knowledge this is the first evaluation of the influence of sex and ethnicity on modafinil pharmacokinetic profile after a single oral dose of modafinil tablets in healthy Chinese volunteers.

METHODS

Study Population

Fifty healthy young male and female volunteers were recruited from Shenyang in Liaoning, Chifeng in Inner Mongolia, Yanji in Jilin, Urumqi in Xinjiang, and Yinchuan in Ningxia, thus comprising the five ethnic groups ($n = 10/\text{group}$). Whose parents, grandparents and adoptive grand-parents all had married within the same ethnicity. All participants were students of the local Medical or Pharmaceutical University who were informed of the objectives, procedures, and risks involved in the study prior to participation. All participants were judged to be healthy according to a pre-study physical examination, which included a medical history and routine biochemical blood analyses. All of the participants' examination data were in the normal range. All medications were forbidden for at least two weeks prior to study participation and alcohol or cigarettes were forbidden for at least 72 h prior to drug administration and for the duration of the testing period. All 25 females were tested during the luteal phase of their menstrual cycle. The study protocol followed the Declaration of Helsinki and was approved by the independent Ethical Committee of the Shenyang Northern Hospital. All participants provided written informed consent prior to enrollment.

Study Design and Procedures

The current study was designed as a single-dose, parallel-group protocol performed in young healthy male and female adults across five different ethnicities in China. Each study phase began at 7:00 a.m. (Beijing Time). All subjects were given uniform diets to follow prior to testing and then fasted overnight prior to modafinil dosing. A single oral dose of a 200 mg modafinil tablets was given with 200 mL of water to each subject. Subjects continued fasting for 2 h following administration. During the test period, all participants remained under close medical supervision and continued the uniform diet.

Blood Sample Collection

Blood samples (4 mL) were collected into heparinized tubes prior to modafinil administration

and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, and 48 h following oral dosage. Samples were immediately centrifuged at 3500 r/min for 8 min, and the plasma was separated and frozen at -25° until analyzed.

Analysis of Plasma Samples

Plasma concentrations of modafinil and modafinil acid were evaluated using HPLC (22). Plasma (0.2 mL) was mixed with 100 μL of internal standard solution, and 0.5 mL of methanol. The mixture was vortex-mixed for 1 min and centrifuged at 15000 r/min for 8 min. Then 20 μL of the supernatant was injected onto a 4.6 mm internal diameter \times 200 mm Diamonsil C_{18} column with ultraviolet detection at 220 nm. The calibration curve showed good linearity over the range of 0.1-10 $\mu\text{g}/\text{mL}$ for modafinil and modafinil acid with intra-day and inter-day relative standard deviations (RSD) of less than 11% at all levels. The relative recoveries of modafinil were $(86.9 \pm 3.5)\%$, $(86.9 \pm 4.2)\%$, and $(96.8 \pm 1.8)\%$ and of modafinil acid were $(98.8 \pm 1.6)\%$, $(92.8 \pm 6.3)\%$, and $(88.3 \pm 5.3)\%$ at 0.2, 1.0, and 8.0 $\mu\text{g}/\text{mL}$ of quality control (QC), respectively.

Statistical Analysis

Statistical analyses were performed by using SPSS software (version 11.5; SPSS Inc., Chicago, IL, USA). For C_{max} , AUC_{0-t} , $\text{AUC}_{0-\infty}$, natural log-transformation of the data was used. Values for T_{max} were compared using nonparametric Wilcoxon two-sample test. Analysis of variance (ANOVA) was used to determine the difference in pharmacokinetic data among ethnicity levels. Comparisons of the pharmacokinetic parameters between different sex levels were evaluated by paired t-test. Descriptive statistics were expressed as mean \pm standard deviation (SD) values. All tests of hypotheses were two-sided, and a P value < 0.05 or < 0.01 was considered statistically significant (23).

RESULTS

Subjects

A total of 50 healthy volunteers participated in this study. One Korean subject withdrew from the study after the drug administration at his own request. The remaining 24 male participants had a mean age of 23 years (range: 19-26), a mean height of 173 cm (range: 162-184), and a mean weight of 66 kg (range: 56-88). The 25 young healthy female participants had a mean age of 22 years (range: 18-24), a mean height of 161 cm (range: 150-167), and a mean weight of 56 kg (range: 44-80). The mean \pm SD values are listed in Table 1.

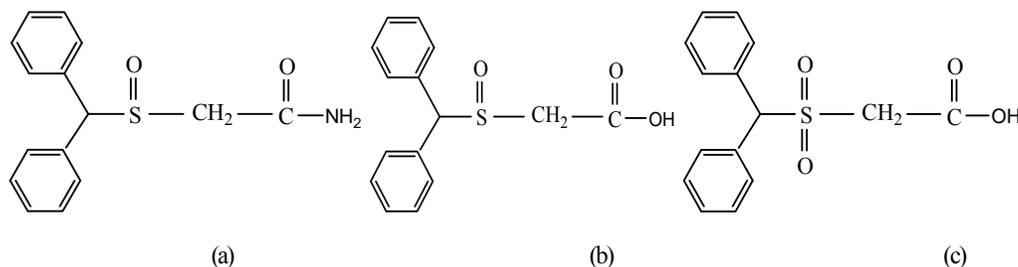


Figure 1. Chemical structures of modafinil (a), modafinil acid (b), and modafinil sulfone (c)

Table 1. Participant Demographics

Ethnicity	Sex	n	Age (y)	Height (cm)	Weight (kg)
Han	M		24.8 ± 0.8	170.4 ± 5.90	64.2 ± 6.1
	F		23.6 ± 0.9	161.2 ± 3.83	53.8 ± 3.6
Mongolia	M		23.8 ± 0.8	174.8 ± 2.59	62.4 ± 3.4
	F		21.8 ± 0.5	160.0 ± 6.82	69.6 ± 15.4
Korea	M		23.0 ± 1.2	178.5 ± 5.97	70.5 ± 8.8
	F		22.2 ± 0.8	156.0 ± 5.29	48.2 ± 4.4
Uygur	M		22.4 ± 0.6	170.4 ± 2.70	66.2 ± 5.8
	F		20.4 ± 1.5	161.8 ± 3.19	52.8 ± 2.8
Hui	M		21.4 ± 1.8	172.0 ± 8.49	69.8 ± 11.8
	F		20.8 ± 1.1	163.6 ± 3.71	53.6 ± 7.6

M, male; F, female; Data are listed as means ± SD.

Safety

No serious adverse events occurred during the study. The one participant withdrew of his own will, and thus, this was not recorded as an adverse event. Nonserious adverse events included the following: One Mongolian participant suffered a headache and fever following administration, but recovered within a day from the symptoms. The most commonly reported adverse events were headache (11/49), nausea (6/49), fever (3/49) and asthenia (22/49). All of the treatment-emergent adverse events were recorded as mild in severity, there was no subjects discontinued from the study due to adverse events. No clinically important changes in respiratory rate, in body temperature, or in physical examination parameters were observed.

Pharmacokinetics

The mean plasma concentration ± SD versus time profiles of modafinil and modafinil acid are shown in Figure 2, 3, 4 and the pharmacokinetic parameters are listed in Tables 2 and 3.

Figure 2 illustrates the mean plasma concentration-time profiles of modafinil and modafinil acid obtained for 49 subjects after administration of a 200 mg oral dose. Both of them

were absorbed rapidly reaching at the maximum concentration of 1.83 ± 0.71 h for modafinil and 2.80 ± 1.06 h after administration. Figure 3 illustrates that the values of C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ for females are obviously larger than that of males for both modafinil and modafinil acid. While the Figure 4 illustrates that except the profile of Korean, the remaining profiles are similar to each other. The profile is not well superimposable, indicating that there might be some sex- or ethnicity-based differences in the pharmacokinetic patterns of modafinil.

Using standard noncompartmental methods to calculate the pharmacokinetic parameters would avoid the different results from the influence of compartment model and its weight, and be better to compare the results with that reported. The results of pharmacokinetic parameters are consistent with those reported by others (24-26) and could be served as the basic of the evaluation for the influence of ethnicity and sex.

Previous clinical studies have indicated that a single oral dose of 200 mg modafinil tablets is therapeutically effective, safe and tolerated (17). There was no unexpected or serious adverse events when modafinil was given to the five study groups.

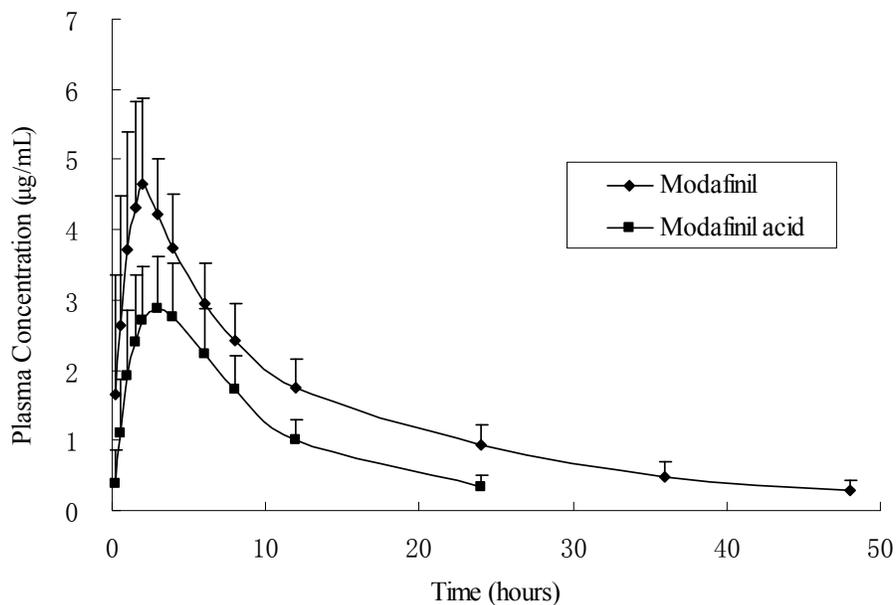


Figure 2. Plasma concentration - time profiles of modafinil and modafinil acid following a single oral administration of a 200 mg modafinil tablets. Each point represents mean \pm SD (n=49)

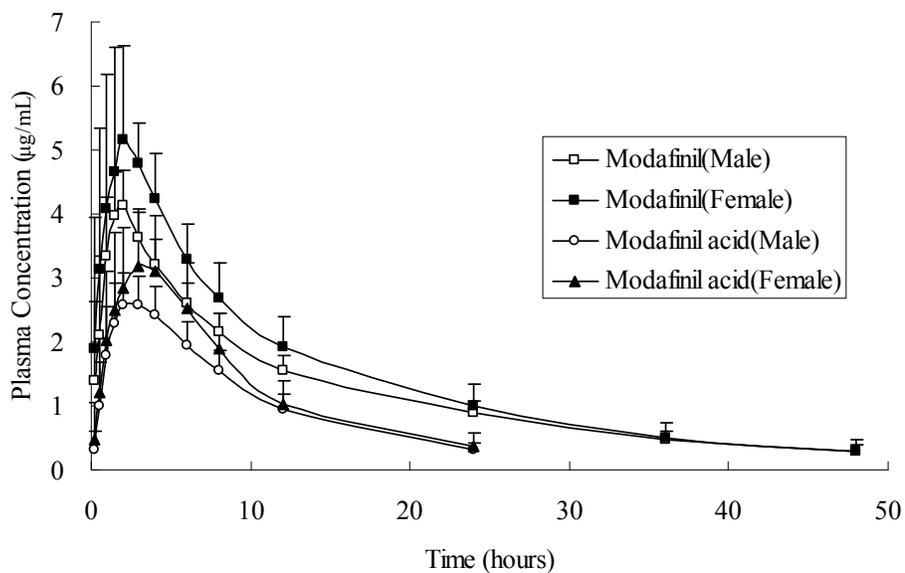


Figure 3. Plasma concentration - time profiles of modafinil and modafinil acid in both sexes. Each point represents mean \pm SD (Male=24, Female=25)

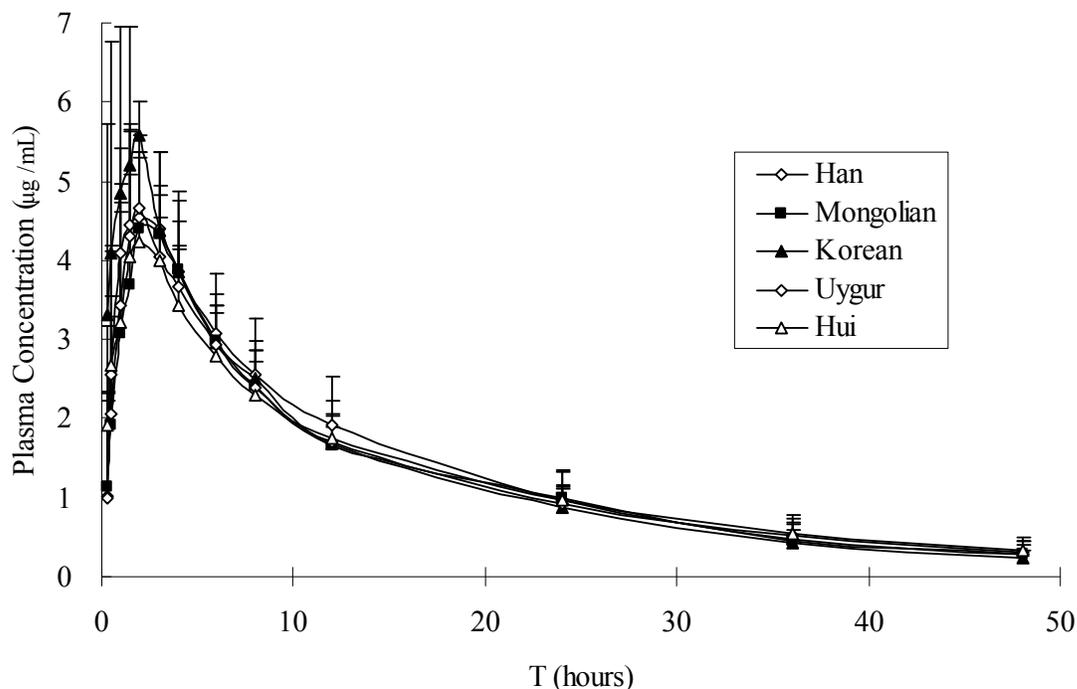


Figure 4. Plasma concentration - time profiles of modafinil in the five ethnicities of China. Each point represents mean \pm SD (Han=10, Mongolian=10, Korean=9, Uygur=10, Hui=10).

Table 2. Mean (\pm SD) Pharmacokinetic Parameters for Modafinil by Ethnicity Following a Single Oral Dose of a 200 mg Modafinil Tablets

Subject	T_{max} (h)	C_{max} (μ g/mL)	$t_{1/2}$ (h)	CL/F (mL/min/kg)	Vd/F (L/kg)	$AUC_{0-\infty}$ (μ g·h/mL)
Han	1.6 \pm 0.7	5.15 \pm 1.08	11.4 \pm 1.5	0.84 \pm 0.15	0.82 \pm 0.11	71.0 \pm 22.6
Mongolian	2.2 \pm 0.8	4.86 \pm 0.67	12.7 \pm 3.2	0.76 \pm 0.11	0.82 \pm 0.19	68.6 \pm 11.6
Korean	1.6 \pm 0.5	5.88 \pm 1.78	11.8 \pm 2.0	0.88 \pm 0.19	0.88 \pm 0.13	69.9 \pm 14.9
Uygur	1.8 \pm 0.5	4.79 \pm 0.68	15.0 \pm 4.0 ^a	0.83 \pm 0.20	1.04 \pm 0.20 ^a	70.9 \pm 15.7
Hui	1.9 \pm 0.9	4.74 \pm 1.01	14.0 \pm 2.1 ^a	0.81 \pm 0.15	0.96 \pm 0.10 ^a	70.6 \pm 20.0

Data are listed as means \pm SD (n=5/group).

^a A significant difference compared with Han ($p < 0.05$).

Similar to previous findings (16), C_{max} , CL/F and $AUC_{0-\infty}$ in healthy young females were higher than those found in males, but Wong YN et al reported that the CL/F of modafinil in females was approximately 22% higher ($p < 0.05$) than that in males, while the current study found no significant difference of CL/F across sexes. However, the results of table 3 indicate that the C_{max} and $AUC_{0-\infty}$ of modafinil and modafinil acid in Chinese were higher than that in Caucasians with the same dose of 200 mg modafinil. And so does the $t_{1/2}$ for both modafinil and modafinil acid which were longer. The possible reason for this difference might be the influence of ethnicity between white Caucasian and

Person of Asian descent which should be further investigated.

The results also indicate that there might be some sex differences among the five groups above according to the values of $t_{1/2}$ and Vd/F. The total amount of modafinil acid detected in the plasma was not similar between young males and females ($p < 0.05$), and the concentration of modafinil acid at 48 h after administration could not be detected. The main pharmacokinetic parameters of modafinil acid were higher in females than in males, regardless of $t_{1/2}$, and the possible reasons about this might be the cytochrome P450(CYP)3A4 is involved in modafinil metabolism, while some

evidence suggests that young women may have approximately 1.4 times the CYP3A4 activity of men(21), so modafinil and modafinil acid eliminate much faster in females than that of males, with shorter $t_{1/2}$ for females than that of males.

In conclusion, the findings from the current

study may indicate that the pharmacokinetic differences exist for modafinil across sex and ethnicity. The shortage of this study is whether the number could stand for the whole population of sex and ethnicity in China, which should be further studied.

Table 3. Mean (\pm SD) Pharmacokinetic Parameters for Modafinil and Modafinil Acid in Young Males and Young Females Compared with Those Previously Reported Following Administration of a Single 200 mg Oral Dose of Modafinil

Parameters	T_{max} (h)	C_{max} (μ g/mL)	$t_{1/2}$ (h)	CL/F (mL/min/kg)	Vd/F (L/kg)	AUC _{0-∞} (μ g·h/mL)
Modafinil						
Wong et al (16)						
Young males	2.0 \pm 1.0	4.21 \pm 0.44	12.7 \pm 3.2	0.72 \pm 0.10	0.77 \pm 0.11	57.0 \pm 7.6
Young females	1.7 \pm 0.9	5.20 \pm 0.83 ^a	10.5 \pm 1.5	0.88 \pm 0.17 ^a	0.78 \pm 0.09	61.3 \pm 12.6
In this study						
Young males	1.8 \pm 0.7	4.33 \pm 0.49	13.8 \pm 3.0	0.81 \pm 0.14	0.95 \pm 0.17	64.1 \pm 10.8
Young females	1.9 \pm 0.8	5.78 \pm 1.13 ^a	12.2 \pm 2.8	0.84 \pm 0.18	0.87 \pm 0.17	76.1 \pm 19.3 ^a
Modafinil acid						
Wong et al (16)						
Young males	2.8 \pm 1.0	2.06 \pm 0.32	5.7 \pm 0.5	NA	NA	22.8 \pm 3.0
Young females	2.9 \pm 0.9	2.65 \pm 0.46 ^a	4.7 \pm 0.5 ^a	NA	NA	22.5 \pm 4.9
In this study						
Young males	2.5 \pm 0.9	2.73 \pm 0.50	7.3 \pm 2.1	NA	NA	32.4 \pm 6.6
Young females	3.0 \pm 1.2	3.47 \pm 0.82 ^a	6.5 \pm 2.2	NA	NA	37.9 \pm 10.2 ^a

NA, not applicable.

a. There was a significant difference between young males and females ($p < 0.05$). The C_{max} and AUC_{0- ∞} of modafinil and modafinil acid were significantly larger ($p < 0.05$, respectively) in the female group compared to the male group. The C_{max} of modafinil was also significantly different across the five ethnicities.

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