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Effects of woohwangcheongsimwon suspension on the pharmacokinetics of bupropion and its active metabolite, 4-hydroxybupropion, in healthy subjects

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Woohwangcheongsimwon suspension has traditionally been used for the treatment and prevention of stroke, hypertension, palpitations, convulsions and unconsciousness in various Asian countries.
- Woohwangcheongsimwon suspensions showed an inhibitory effect on CYP2B6 activity *in vitro*. Two terpenoids, borneol and isoborneol, are major constituents of woohwangcheongsimwon suspension, and show a competitive inhibition of CYP2B6 with K_i values of 9.5 and 5.9 μM, respectively.
- Bupropion undergoes metabolic transformation to the active metabolite, 4-hydroxybupropion, primarily via CYP2B6 both *in vivo* and *in vitro*. It is often used as a CYP2B6 substrate for clinical drug–drug interaction studies.
- Drug interactions may occur between woohwangcheongsimwon suspension and bupropion.

WHAT THIS STUDY ADDS

- Co-administration with woohwangcheongsimwon suspension did not alter the pharmacokinetics of bupropion or its metabolite, 4-hydroxybupropion.
- Dosage adjustment of bupropion is unnecessary in patients concomitantly administered the highest recommended daily dose of woohwangcheongsimwon suspension.

AIMS

To examine the effects of woohwangcheongsimwon suspension on the pharmacokinetics of bupropion and its active metabolite, 4-hydroxybupropion, formed via CYP2B6 *in vivo*.

METHODS

A two-way crossover clinical trial with a 2 week washout period was conducted in 14 healthy volunteers. In phases I and II, subjects received 150 mg bupropion with or without woohwangcheongsimwon suspension four times (at −0.17, 3.5, 23.5 and 47.5 h, with the time of bupropion administration taken as 0 h) in a randomized balanced crossover order. Bupropion and 4-hydroxybupropion plasma concentrations were measured for up to 72 h by LC-MS/MS. Urine was collected up to 24 h to calculate the renal clearance. In addition, the *CYP2B6**6 genotype was also analyzed.

RESULTS

The geometric mean ratios and 90% confidence interval of bupropion with woohwangcheongsimwon suspension relative to bupropion alone were 0.976 (0.917, 1.04) for AUC$(0,\infty)$ and 0.948 (0.830,1.08) for C_{max}, respectively. The corresponding values for 4-hydroxybupropion were 0.856 (0.802, 0.912) and 0.845 (0.782, 0.914), respectively. The t_{max} values of bupropion and 4-hydroxybupropion were not significantly different between the two groups ($P > 0.05$). The pharmacokinetic parameters of bupropion and 4-hydroxybupropion were unaffected by woohwangcheongsimwon suspension.

CONCLUSIONS

These results indicate that woohwangcheongsimwon suspension has a negligible effect on the disposition of a single dose of bupropion *in vivo*. As a result, temporary co-administration with woohwangcheongsimwon suspension does not seem to require a dosage adjustment of bupropion.

Table 1

The major ingredients of woohwangchengonsimwon suspension (Kwang-Dong Pharmaceutical Company, Seoul, Korea)

Ingredients	Quantity in 30 ml (mg)
Bovis Calculus	14
Dioscoreae Rhizoma	282
Glycyrrhizae Radix et Rhizoma	202
Ginseng Radix	97
Typhae Pollen	100
Massa Medicata Fermentata	100
Glycine Semen Germinatum	70
Cinnamomi cortex	70
Paeoniae Radix	60
Liriopis Tuber	60
Scutellariae Radix	60
Angelicae Gigantis Radix	60
Saposhnikoviae Radix	60
Atractylodis Rhizoma Alba	60
Bupleuri Radix	50
Platycodonis Radix	50
Armeniacae Semen	50
Poria Sclerotium	50
Cnidii Rhizoma	50
Civet	15
Antelopis Cornu	35
Borneolum*	41
Ampelopsis Radis	30
Zingiberis Rhizoma	30

*Borneolum included 38.58 mg of borneol and isoborneol.

Introduction

Woohwangcheongsimwon suspension (sometimes called 'uwhangchungsimwon'), composed of 24 medicinal herbs (listed in Table 1), is a commonly used herbal medicine in Korea and other East Asian countries. Its original formulation was in a tablet form. It has been officially listed in the Korean Pharmaceutical Codex for a long time and an aqueous suspension has recently been developed for convenient administration [1]. It has been widely used for treatment and prevention of stroke, hypertension, palpitations, convulsions and unconsciousness [2]. In Korea, woohwangcheongsimwon suspension can easily be obtained over the counter in local pharmacies; nowadays, it is often preferred as a preventive medicine rather than a treatment.

Our previous studies have reported that woohwangcheongsimwon suspension inhibited CYP2B6 activity *in vitro*. Two terpenoids, borneol and isoborneol, are major constituents of woohwangcheongsimwon suspension, and show competitive inhibition of CYP2B6, with K_i values of 9.5 and 5.9 μM, respectively [2]. Furthermore, we found that other monoterpenes, such as citral and geraniol, have inhibitory potency on CYP2B6-catalyzed bupropion 4-hydroxylation as well as isoborneol and borneol [3]. These findings suggested that a drug interaction study of woohwangcheongsimwon and CYP2B6 substrates in humans should be undertaken.

Bupropion is a monocyclic aminoketone that was first used as an antidepressant and subsequently found to be effective as an antismoking agent [4]. CYP2B6 is the major enzyme involved in biotransformation of bupropion to its active metabolite, 4-hydroxybupropion both *in vivo* and *in vitro* [5–10]. Several studies have examined the interaction between bupropion as a probe substrate of CYP2B6 and other medications [7–10]. Rifampicin treatment increases apparent clearance of bupropion by inducing CYP2B6 *in vivo* [7], whereas concomitant use of ticlopidine or clopidogrel significantly inhibits CYP2B6-catalyzed bupropion 4-hydroxylation [8]. At high plasma concentrations, bupropion use increases the risk of seizure as a side-effect [11], which may be clinically important when bupropion is used with other drugs that affect its metabolism.

Although woohwangcheongsimwon is one of the most commonly used herbal medications in Korea, no clinical studies have been performed to determine the effect of woohwangcheongsimwon suspension on CYP2B6 activity or interactions with other drugs. The purpose of this study was to investigate whether woohwangcheongsimwon suspension inhibits CYP2B6-catalyzed bupropion 4-hydroxylation in healthy male volunteers.

Methods

Subjects

Fourteen male subjects, each within 20% of their ideal body weight calculated by Broca's formula, were enrolled in this study (age mean ± SD = 28.8 ± 4.83 years; weight 70.0 ± 7.45 kg) [12]. All volunteers were determined healthy based on medical history, physical examination, vital signs and clinical laboratory tests performed 2 weeks or less before the start of the study. They were non-smokers, ate a normal diet, and none was a user of botanical supplements.

Subjects were instructed to refrain from alcohol, caffeine, fruit juice and cruciferous vegetables throughout the study, and these limitations were further emphasized 1 week before probe drug administration. Subjects were also asked to abstain from taking prescription and over the counter medications for 2 weeks before and during the study period.

The study protocol was approved by the Institutional Review Board of Inje University Busan Paik Hospital, Busan, Korea. In addition, all participants provided written informed consent prior to enrolment in this study.

CYP2B6 genotyping

CYP2B6 genotyping was performed by pyrosequencing of polymerase chain reaction (PCR) products as described previously [13]. Commonly accepted *CYP2B6* alleles consisting of a combination of the nucleotides at cDNA posi-

tions 516 and 785 were assessed; the wild-type allele *CYP2B6*1* was defined as 516G/785A, while *CYP2B6*6* was defined as 516T/785G.

Study design

This study had an open-label, two-treatment crossover and randomized design with two phases. All doses of sustained-release bupropion 150 mg (Wellbutrin SR, GlaxoSmithKline, Research Triangle Park, NC) and each bottle (30 ml) of woohwangcheongsimwon suspension manufactured in compliance with the Korean Pharmaceutical Codex (Kwang-Dong Pharmaceutical Company, Seoul, Korea) were administered by study personnel with a standard low-fat meal. In phases I and II, in randomized balanced crossover order, subjects received a dose of 150 mg bupropion alone as a control phase or 150 mg bupropion plus four doses of woohwangcheongsimwon suspension reflecting its maximal daily dosage at −0.17, 3.5, 23.5 and 47.5 h, with the time of bupropion administration taken as 0 h. In addition, a 2 week washout period was imposed between the two phases. Safety monitoring was performed throughout the study.

Blood and urine sampling

Venous blood samples (5 ml each) were collected in lithium heparin tubes drawn from forearm venous catheters before drug administration on the first day of the study and following specified doses of bupropion alone and bupropion plus woohwangcheongsimwon suspension. Sampling for bupropion and its metabolite, 4-hydroxybupropion, was performed before and at 1, 2, 3, 4, 5, 6, 7, 8, 12, 24, 48 and 72 h after bupropion administration on study day 1 in each phase. A spot of urine was collected as a blank sample before trial drug administration, and then urine was collected until 24 h after bupropion administration. After collection, plasma was separated by centrifugation at 3000 rev min^{-1} for 10 min at 4°C. The plasma was transferred into cryovials and stored at −80°C until analysis. Urine was also stored at −80°C after measuring its volume.

LC-MS/MS analysis of bupropion and 4-hydroxybupropion

Plasma or urine samples were analyzed for bupropion and 4-hydroxybupropion concentration using our LC-MS/MS method. Briefly, samples were prepared by a simple deproteinization procedure involving the addition of 0.2 ml of acetonitrile containing 0.2 μM phenacetin as an internal standard to 0.1 ml of plasma sample. Chromatographic separation was carried on a reversed-phase column (Luna phenyl-hexyl 2.0 mm i.d. × 100 mm, 3 μm particle size; Phenomenex, Torrance, CA), with an isocratic mobile phase consisting of acetonitrile and distilled water containing 0.1% formic acid (60:40, v : v), a flow rate of 0.2 ml min^{-1} and a total run time of 3.0 min per sample. Detection and quantification were performed using a mass spectrometer in the selected reaction-monitoring mode with positive electrospray ionization at *m/z* 240 → 184 for bupropion, *m/z* 256 → 238 for 4-hydroxybupropion and *m/z* 180 → 110 for phenacetin. The TurbolonSpray interface was operated in positive ion mode at 5500 V and 500°C. The operating conditions were as follows: nebulizing gas flow, 8 l min^{-1}; curtain gas flow, 10 l min^{-1}; collision gas (nitrogen) pressure, medium; collision energy, 25 eV. Quadrupoles Q1 and Q3 were set on unity resolution. The analytical data were processed using Analyst software (version 1.4, Applied Biosystems, Foster City, CA). The assay was linear over a concentration range of 0.4–200 ng ml^{-1} with a lower limit of quantification of 0.4 ng ml^{-1} for bupropion and 1–500 ng ml^{-1} with a lower limit of quantification of 1 ng ml^{-1} for 4-hydroxybupropion, respectively, in human plasma. Inter-day and intra-day coefficients of variation were less than 15% for both analytes. No relevant cross-talk or matrix effect was observed. Urine samples were diluted up to 50-fold with acetonitrile containing an internal standard following the same preparation. To determine total 4-hydroxybupropion, β-glucuronidase from *Helix pomatia* (2500 units ml^{-1} in 0.2 M acetate buffer, pH 5.0; Sigma-Aldrich, St Louis, MO) was added to a 10 μl aliquot of urine [14]. The mixture was manually mixed and incubated in a water-bath shaker kept at 37°C and at a rate of 50 oscillations min^{-1} for 2 h. Other procedures were similar to those of plasma samples.

Pharmacokinetic analysis

The pharmacokinetic parameters of bupropion and 4-hydroxybupropion were calculated by noncompartmental analysis techniques using WinNonlin Professional software (version 5.2; Pharsight Corporation, Mountain View, CA). The peak plasma concentration (C_{max}) values and time to reach C_{max} (t_{max}) were obtained directly from the observed plasma concentration–time data. The elimination rate constant (λ_z) was estimated from the least-squares regression slope of terminal plasma concentrations. The area under the plasma concentration–time curve (AUC(0,72 h) from time 0 to the last measurement was calculated according to the log-linear trapezoidal rule. The AUC(0,∞) from time 0 to infinity was calculated as $AUC(0,\infty) = AUC(0,72\ h) + C_{72}/\lambda_z$, where C_{72} is the plasma concentration measured 72 h after drug administration. The half-life ($t_{1/2}$) of bupropion and 4-hydroxybupropion was calculated as $0.693/\lambda_z$, the oral clearance of bupropion (CL/*F*) was calculated as dose/AUC(0,∞). The renal clearance (CL_R) was calculated as the ratio of Ae to AUC(0,∞), where Ae is the amount of bupropion excreted as unchanged drug into the urine within 24 h.

Safety assessment

Safety was evaluated throughout the clinical study based on adverse event (AE) monitoring, clinical laboratory values, vital sign measurements and physical examination findings.

Table 2

Pharmacokinetic parameters (mean ± SD) of bupropion and 4-hydroxybupropion after oral administration of bupropion 150 mg with or without woohwangcheongsimwon suspension to healthy male volunteers

	Bupropion alone (n = 14)	+ Woohwangcheongsimwon (n = 14)	Geometric mean ratios (90% CI)	P value
Bupropion				
AUC(0,∞) (ng ml^{-1} h)	991.0 ± 218.6	967.3 ± 219.0	0.976 (0.917, 1.04)	
$t_{1/2}$ (h)	17.9 ± 4.70	16.9 ± 4.75	0.935 (0.864, 1.01)	
CL/F (l h^{-1})	164 ± 56.7	167 ± 57.8	1.02 (0.950, 1.09)	
C_{max} (ng ml^{-1})	105 ± 26.4	101 ± 34.5	0.948 (0.830, 1.08)	
t_{max} (h)	3 (1–5)*	3 (1–5)*		NS†
CL_R (l h^{-1})	0.374 ± 0.210	0.436 ± 0.285	1.13 (0.823, 1.56)	
4-hydroxybupropion				
AUC(0,∞) (ng ml^{-1} h)	15123 ± 4060.2	12922 ± 3542.4	0.856 (0.802, 0.912)	
$t_{1/2}$ (h)	20.9 ± 3.57	20.9 ± 3.84	0.999 (0.960, 1.04)	
C_{max} (ng ml^{-1})	405 ± 84.6	344 ± 84.2	0.845 (0.782, 0.914)	
t_{max} (h)	6 (4–12)*	7 (5–12)*		NS†
Ae, free (%)‡	0.611 ± 0.263	0.515 ± 0.183	0.915 (0.774, 1.08)	
Ae, total (%)§	3.04 ± 0.777	2.59 ± 0.771	0.892 (0.796, 1.00)	

*Median (ranges). †Not significant. ‡Percentage of the bupropion dose excreted as free (unconjugated) form of 4-hydroxybupropion in the 24 h urine. §Percentage of the bupropion dose excreted as total form of 4-hydroxybupropion in the 24-h urine.

Statistical analysis

Study sample sizes were determined from variance estimates based on prior bupropion pharmacokinetic data. To determine clinically relevant interactions, we used the bioequivalence approach [15]. Geometric means were calculated for the AUC(0,∞), C_{max} and so on of bupropion and 4-hydroxybupropion. Geometric mean ratios (GMRs) with 90% confidence intervals (CIs) were calculated after log transformation of within-subject data. In addition, comparison of the t_{max} for the different treatment groups *in vivo* was performed using the Wilcoxon signed-rank test. All statistical analyses were performed with the SAS software package (version 9.1.3; SAS Institute, Cary, NC) and $P < 0.05$ was considered statistically significant. The results are expressed as the means ± standard deviation (SD), with the exception of t_{max}, which is expressed as the median (range).

Results

All 14 subjects completed both phases according to the study protocol. None of the subjects reported any remarkable side-effects during the study period. No clinically significant alterations in blood pressure, heart rate or body temperature were observed.

Mean plasma concentration–time profiles of bupropion and 4-hydroxybupropion with or without woohwangcheongsimwon suspension were very similar, and some relevant pharmacokinetic parameters of bupropion and 4-hydroxybupropion are summarized in Table 2. As shown in Table 2, pharmacokinetic parameters of bupropion and 4-hydroxybupropion were comparable between the two groups. The GMR and 90% CI of bupropion with woohwangcheonsimwon suspension relative to bupropion alone were 0.976 (0.917, 1.04) for AUC(0,∞) and 0.948 (0.830, 1.08) for C_{max}, respectively. The corresponding values for 4-hydroxybupropion were 0.856 (0.802, 0.912) and 0.845 (0.782, 0.914), respectively. The t_{max} of bupropion and 4-hydroxybupropion were not significantly different between the two groups ($P > 0.05$). Woohwangcheongsimwon suspension did not seem to affect the pharmacokinetic parameters of bupropion or 4-hydroxybupropion. In addition, the results of *CYP2B6* genotyping indicated that our study population included two *CYP2B6*1/*6* and 12 wild-type subjects, although this was insufficient to elucidate the interindividual differences in pharmacokinetic parameters (data are not shown). The percentage of the oral dose of bupropion excreted in 24 h urine samples as intact drug was almost negligible in both groups. The Ae values of both free (unconjugated) and total 4-hydroxybupropion were comparable between the two groups (Table 2). The ratios of $Ae_{free\ 4\text{-}hydroxybupropion}$: $Ae_{total\ 4\text{-}hydroxybupropion}$ were 0.200 ± 0.0567 and 0.201 ± 0.0576 for bupropion alone and co-administration with woohwangcheongsimwon suspension, respectively, suggesting that glucuronidation activity was not changed by co-administration of woohwangcheongsimwon.

Discussion

In this study, we examined the CYP2B6 inhibitory effects of woohwangcheongsimwon suspension on the pharmacokinetics of bupropion. The maximum recommended daily dose (two bottles per day) of woohwangcheongsimwon suspension was assessed to maximize the CYP2B6 inhibitory potential of the woohwangcheongsimwon suspension. To avoid confounding factors in this study, male,

healthy, non-smoking subjects were selected, as oral contraceptives and smoking have been reported to affect CYP2B6 activity [9, 16]. In previous studies, only moderate changes in the AUC or C_{max} of bupropion were observed with use of ticlopidine or clopidogrel, both of which are potent CYP2B6 inhibitors [8]. In addition, the *CYP2B6**6 allele, which is associated with reduced CYP2B6 activity, did not change the AUC or C_{max} of bupropion compared with the wild type, although some alterations were observed in those of 4-hydroxybupropion [17]. As alternative metabolic pathways become progressively more important when the biotransformation to 4-hydroxybupropion is blocked, these alternative ketone-reduction pathways leading to the formation of the erythro-hyrdrobupropion and threo-hydrobupropion seem not to be mediated by CYP. Therefore, for CYP2B6 phenotyping purposes, quantification of the extent of 4-hydroxybupropion formation is necessary [8].

Our results show that the maximum recommended daily dose of woohwangcheongsimwon suspension had no effect on the pharmacokinetics of bupropion or 4-hydroxybupropion. Co-administration with woohwangcheongsimwon did not result in clinically meaningful changes in exposure (AUC) of bupropion and 4-hydroxybupropion, as the 90% CIs for the ratio of geometric means were contained within the commonly applied no-effect bounds of 0.8, 1.25 (Table 2). The metabolic ratios, calculated as the AUC ratio of 4-hydroxybupropion to bupropion, did not differ between the two groups: 15.8 $\pm$ 4.62 and 13.8 $\pm$ 4.12 in the absence and presence of woohwangcheongsimwon suspension, respectively. This suggests that woohwangcheongsimwon suspension does not alter CYP2B6 activity determined by 4-hydroxylation of bupropion *in vivo*.

There is a limitation in explaining the dosing interval of woohwangcheongsimwon in the absence of available information on its pharmacokinetic properties. We designed the experiment to maximize the inhibitory effects of woohwangcheongsimwon as in other drug–drug interaction studies, based on the maximum inhibitory dosage, within the recommended daily dosage. Considering the practical use of woohwangcheongsimwon for acute treatment, we applied the third and fourth dosages afterwards. A bottle of woohwangcheongsimwon suspension contains a total of 38.58 mg of borneol and isoborneol (Table 1). To our knowledge, no information is available regarding the bioavailability of either in humans. However, we postulated that their bioavailabilities would be low, based on the results of previous studies with other monoterpenes such as 1,8-cineole [18, 19]. We did not determine plasma concentrations of borneol and isoborneol after oral administration of woohwangcheongsimwon suspension. However, the plasma concentrations of borneol and isoborneol after administration of woohwangcheongsimwon suspension are likely lower than their K_i values, and therefore, do not have an effect *in vivo*. In summary, the results of the present study indicate that the maximum daily dose of woohwangcheongsimwon suspension has little inhibitory effect on CYP2B6-catalyzed 4-hydroxylation of bupropion *in vivo*.

Competing interests

There are no competing interests to declare.

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