Rapid clinical induction of bupropion hydroxylation by metamizole in healthy Chinese men

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Bupropion, an antidepressant and smoking cessation drug, is metabolized to its active metabolite, 4-hydroxybupropion, almost exclusively by CYP2B6.
- Metamizole, a pyrazolone derivative with analgesic properties, was shown in an *in vitro* study to increase significantly the expression of CYP2B6 and bupropion hydroxylase activity.
- The effect of metamizole on bupropion hydroxylation has not been investigated and drug interactions may occur between metamizole and bupropion.

WHAT THIS PAPER ADDS

- Oral administration of metamizole for 4 days significantly altered the pharmacokinetics of both bupropion and its active metabolite, 4-hydroxybupropion, and significantly increased the CYP2B6-catalyzed bupropion hydroxylation in all of the subjects.
- Dosage adjustment of bupropion may be needed in patients when metamizole is concomitantly administered.

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AIMS

This study aimed to investigate the effect of metamizole on bupropion hydroxylation related to different CYP2B6 genotype groups in healthy volunteers.

METHODS

Sixteen healthy male volunteers (6 CYP2B6*1/*1, 6 CYP2B6*1/*6 and 4 CYP2B6*6/*6) received orally administered bupropion alone and during daily treatment with metamizole 1500 mg day⁻¹ (500 mg tablet taken three times daily) for 4 days. Serial blood samples were obtained up to 48 h after each bupropion dose.

RESULTS

After metamizole treatment relative to bupropion alone, the geometric mean ratios (GMRs) and 90% confidence interval (CI) of the AUC(0,∞) ratio of 4-hydroxybupropion over bupropion were 1.99 (1.57, 2.55) for the CYP2B6*1/*1 group, 2.15 (1.53, 3.05) for the CYP2B6*1/*6 group and 1.86 (1.36, 2.57) for the CYP2B6*6/*6 group. The GMRs and 90% CI of bupropion were 0.695 (0.622, 0.774) for AUC(0,∞) and 0.400 (0.353, 0.449) for C_{max}, respectively. The corresponding values for 4-hydroxybupropion were 1.43 (1.28, 1.53) and 2.63 (2.07, 2.92). The t_{1/2} value was significantly increased for bupropion and decreased for 4-hydroxybupropion. The t_{max} values of bupropion and 4-hydroxybupropion were both significantly decreased. The mean percentage changes in pharmacokinetic parameters among the CYP2B6 genotype groups were not significantly different.

CONCLUSIONS

Oral administration of metamizole for 4 days significantly altered the pharmacokinetics of both bupropion and its active metabolite, 4-hydroxybupropion, and significantly increased the CYP2B6-catalyzed bupropion hydroxylation in all of the subjects. Cautions should be taken when metamizole is co-administered with CYP2B6 substrate drugs.

Introduction

Although it has been withdrawn from the USA, UK, Sweden and Denmark due to severe adverse effects, metamizole is still widely available in Spain, Poland, Bulgaria, Africa, Russia, Latin, India and South America as an effective antipyretic and analgesic drug [1–3]. Currently, metamizole is still produced by many companies in China approved by SFDA (State Food and Drug Administration, <http://www.sda.gov.cn/WS01/CL0001/>) and widely used despite its potential adverse effects. The results of clinical interaction studies of metamizole could lead to pharmacovigilance in prescription information for patients taking metamizole. As far as we know, the only interaction study of metamizole in humans revealed a significant decrease in ciclosporin blood concentrations during short term administration of metamizole [4]. The potential mechanism was proven to be inductive effects of metamizole on cytochrome P450 (CYP) 3A4 [5].

Previous study has indicated that metamizole selectively induced CYP2B in rats [6]. Analysis of liver microsomes from patients treated with an average dosage of 1–2 g metamizole day⁻¹ revealed 3.8-fold higher expression of CYP2B6 and 2.9-fold higher bupropion hydroxylase activity compared with untreated subjects [5]. Also, liver samples from individuals with and without metamizole treatment who were CYP2B6*1/*1 exhibited at least a 2.5-fold higher CYP2B6 expression and bupropion-hydroxylase activity compared with individuals with one or two CYP2B6*6 alleles [5].

Inductive or inhibitive effects on CYP2B6 activity identified by bupropion hydroxylation have been extensively studied [7–13], which might lead to potential drug interactions and result in unexpected clinical consequences. Until now, the effect of metamizole administration on CYP2B6-metabolized bupropion hydroxylation in humans has not previously been reported. The present study was conducted to investigate the effect, if any, of short term metamizole use on CYP2B6-catalyzed bupropion hydroxylation and to describe the clinical interaction between bupropion and metamizole in healthy volunteers related to different CYP2B6*6 genotypes.

Methods

Subjects

The study protocol was approved by the ethics committee of Central South University, Changsha, Hunan, P. R. China and registered in the Chinese Clinical Trial Registry (registration number: ChiCTR-TNRC-10001118). A total of 245 participants were successfully genotyped. Sixteen healthy, non-smoking male volunteers with specific CYP2B6 genotypes (six CYP2B6*1/*1, nine CYP2B6*1/*6 and four CYP2B6*6/*6) were enrolled in the clinical trial after having given written informed consent (aged 20 to 23 years

weight range, 62–85 kg, body mass index range 21–26 kg m⁻²). The subjects were ascertained to be in good health by medical history, a full clinical examination and standard haematologic and blood chemical laboratory tests before enrollment. Any regular medication, alcohol, soft drinks, smoking and caffeine-containing beverages, any vitamins and nutritional supplements were refrained from for 2 weeks before study commencement and throughout the study. All of the subjects were told about potential adverse effects of metamizole.

CYP2B6 genotyping

CYP2B6*6 was detected in a haplotype assay using a two-step allele-specific polymerase chain reaction (PCR) as described previously [14]. Selected samples were sequenced according to a standard protocol with ABI PRISM Big Dye Terminator Cycle Sequencing Ready Reaction Kit and ABI 3700 DNA Analyzer (Applied Biosystems, Foster City, California, USA). The same primers as for the PCR amplification were used.

Study design

This study was carried out in a two phase, two treatment, sequential manner. After an overnight fast, subjects ingested a single oral dose of 150 mg bupropion (two tablets of 75 mg Zyban SR; WanTe, Hainan, China) with 200 ml water on day 1. Blood samples for pharmacokinetic analysis were taken for 2 days post dose. After a 7 day washout period, subjects received for 4 days administration of metamizole sodium tablets of the same batch (500 mg three times daily; Hu Bei Hua Zhong Pharmaceutical Co., Xiangfan, China), on days 8 to 11. On day 12, a single 150 mg oral dose of bupropion was then administered after overnight fasting. Four hours after bupropion ingestion, they had access to water and breakfast. Telephone follow-up every other day with investigators was performed to ensure compliance and detect adverse effects. Routine screening for blood (including red blood cells, white blood cells, haemoglobin and platelets) and for urine (including urine protein, urine sugar, urine red blood cells, urine white blood cells, catheter type, urobilinogen and urine bilirubin) were tested before and 1 week, 1, 2, 3 and 6 months after the experiments.

Blood sampling

Serial blood samples (5 ml) were collected from an in-dwelling venous catheter (anticoagulated with sodium heparin) before and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36 and 48 h after bupropion ingestion. Blood samples were collected in plastic containers and immediately centrifuged. The separated plasma samples were immediately frozen at –20°C until assay.

Assay

Concentrations of bupropion and 4-hydroxybupropion in plasma were determined using validated liquid chroma-

tography with tandem mass spectrometric detection (LC/MS/MS) method. The assay of plasma concentrations of bupropion and 4-hydroxybupropion was performed by liquid chromatography–mass spectrometry with the Finnigan LCQ Deca XPplus (Finnigan, San Jose, CA, USA). A Kromasil C18 column (5 μ m, 150 $\times$ 4.6 mm) and a mobile phase (acetonitrile : 0.1% ammonium acid : 20 mM ammonium formate = 4 : 3 : 3) at a flow rate of 0.2 ml min⁻¹ were applied. Talinolol was used as the internal standard. The ion transitions monitored were as follows: m/z 239 to 184 for bupropion, m/z 256 to 238 for 4-hydroxybupropion and m/z 260 to 183 for talinolol. These transitions represent the product ions of the [M + H]⁺ ions. The lower limits of quantification for bupropion and 4-hydroxybupropion were 5.684 and 6.83 ng ml⁻¹ and the assay ranges used were 5.684–1455 and 6.831–2188 ng ml⁻¹, respectively. The correlation coefficient for bupropion calibration curves was 0.993 and for 4-hydroxybupropion 0.997. The highest bupropion and 4-hydroxybupropion plasma concentrations measured were 452.7 and 688.4 ng ml⁻¹. The intraday and interday coefficients of variation (CVs) for the low and high quality control samples were less than 5%.

Pharmacokinetic analysis

The maximum plasma concentration ($C_{\max}$) and the time to $C_{\max}$ ($t_{\max}$) were obtained by inspection of the concentration–time data. The AUC to the last quantifiable concentration AUC(0, t) was determined by use of the linear trapezoidal rule. λ_z is the elimination rate constant determined from the terminal slope of the log concentration–time plot. The apparent terminal half life ($t_{1/2}$) was calculated as $0.693/\lambda_z$. The area under the concentration–time curve extrapolated to infinity AUC(0, ∞) was calculated as $AUC(0, \infty) = AUC_{0-48} + C_{48}/\lambda_z$, where C_{48} is the plasma concentration measured 48 h after drug administration. The AUC(0, ∞) ratio of 4-hydroxybupropion : bupropion was expressed as AUC_{hyd} : AUC_{bup}. The oral clearance (CL/F) of bupropion was calculated by dividing the bupropion dose by the AUC of bupropion and the subject's weight.

Statistical analysis

The bioequivalence approach was used to determine clinically relevant interactions [15]. The pharmacokinetic parameters with and without metamizole treatment were compared by use of a two-tailed paired *t*-test after logarithmic transformation. Geometric mean ratios (GMRs) with 90% confidence intervals (CIs) were calculated after log transformation of within subject ratios for pharmacokinetic variables for bupropion and 4-hydroxybupropion. The between treatment $t_{\max}$ was compared by use of the Wilcoxon signed rank test. The mean changes in pharmacokinetic parameters among the CYP2B6 genotype groups were compared using one way ANOVA. The results are expressed as the means $\pm$ standard deviation (SD) in the text and tables and as mean $\pm$ standard error (SE) in the

Figure 1

Plasma concentration–time profiles of bupropion (A) and 4-hydroxybupropion (B) after single oral dose alone (○) or during treatment with metamizole (▲). Data for 16 healthy subjects are presented as mean $\pm$ SE

figures, with the exception of $t_{\max}$, which is expressed as the median (range). Statistical calculations were performed with SPSS for Windows, version 11.5 (SPSS Inc., Chicago, IL, USA) and *P* values <0.05 were considered significant.

Results

No serious drug-related adverse events occurred during and after the investigation. All of the volunteers successfully completed the study.

As shown in Figure 1 and Table 1, metamizole treatment significantly decreased bupropion $C_{\max}$ by 60% (90% CI 55, 65%) and AUC(0, ∞) of bupropion by 31% (90% CI 23, 38%), and significantly increased 4-hydroxybupropion $C_{\max}$ by 163% (90% CI 107, 192%) and AUC(0, ∞) of 4-hydroxybupropion by 43% (90% CI 28, 53%). The apparent terminal $t_{1/2}$ was significantly increased for bupropion by 35% (90% CI 22, 49%) and decreased for 4-

Table 1

Pharmacokinetic parameters (mean $\pm$ SD) of bupropion and 4-hydroxybupropion after single oral dose of 150 mg bupropion alone or co-administered with daily metimazole in healthy subjects with different CYP2B6 genotypes

Parameter	CYP2B6*1/*1 (n = 6)				CYP2B6*1/*6 (n = 6)				CYP2B6*6/*6 (n = 4)			
	Bupropion alone	Bupropion and metimazole administration	Geometric mean ratios (90% CI)	Bupropion alone	Bupropion and metimazole administration	Geometric mean ratios (90% CI)	Bupropion alone	Bupropion and metimazole administration	Bupropion alone	Bupropion and metimazole administration	Geometric mean ratios (90% CI)	
Bupropion												
AUC(0 ∞) (ng ml ⁻¹ h)	1870 $\pm$ 740.0	1262 $\pm$ 530.8	0.662 (0.521, 0.837)*	1922 $\pm$ 664.3	1329 $\pm$ 550.0	0.692 (0.563, 0.851)*	2065 $\pm$ 595.2	1622 $\pm$ 797.2	2065 $\pm$ 595.2	1622 $\pm$ 797.2	0.752 (0.574, 0.980)	
C _{max} (ng ml ⁻¹)	181.1 $\pm$ 73.0	71.7 $\pm$ 18.7	0.409 (0.341, 0.490)*	174.1 $\pm$ 40.2	72.4 $\pm$ 29.0	0.401 (0.287, 0.553)*	207.6 $\pm$ 51.3	81.8 $\pm$ 29.8	207.6 $\pm$ 51.3	81.8 $\pm$ 29.8	0.383 (0.318, 0.458)*	
t _{max} (h)†	1 (1–1.5)†	1 (0.5–1.5)†		1.5 (0.5–1.5)†	1 (0.5–1.5)†		1.5 (1–2)†	1 (0.5–1.5)†	1.5 (1–2)†	1 (0.5–1.5)†		
t _{1/2} (h)	10.9 $\pm$ 1.17	14.6 $\pm$ 1.79	1.34 (1.15, 1.57)*	12.9 $\pm$ 4.78	18.4 $\pm$ 12.4	1.31 (1.10, 1.58)*	11.9 $\pm$ 3.23	17.1 $\pm$ 6.06	11.9 $\pm$ 3.23	17.1 $\pm$ 6.06	1.40 (0.42, 2.14)	
CL/F (l h ⁻¹ kg ⁻¹)	1.36 $\pm$ 0.47	2.10 $\pm$ 0.93	1.51 (1.19, 1.91)*	1.32 $\pm$ 0.62	1.85 $\pm$ 0.57	1.63 (1.36, 1.95)*	1.15 $\pm$ 0.39	1.57 $\pm$ 0.59	1.15 $\pm$ 0.39	1.57 $\pm$ 0.59	1.18 (0.92, 1.53)	
4-hydroxybupropion												
AUC(0 ∞) (ng ml ⁻¹ h)	15081 $\pm$ 8913.1	20280 $\pm$ 13621	1.32 (1.17, 1.48)*	13248 $\pm$ 4321.3	19346 $\pm$ 5297	1.49 (1.18, 1.88)*	14602 $\pm$ 6933.2	20364 $\pm$ 10148	14602 $\pm$ 6933.2	20364 $\pm$ 10148	1.40 (1.21, 1.63)*	
C _{max} (ng ml ⁻¹)	220.6 $\pm$ 87.7	593.6 $\pm$ 363.9	2.54 (1.94, 3.31)*	352.3 $\pm$ 191.0	997.8 $\pm$ 469.0	2.86 (2.08, 3.94)*	315.9 $\pm$ 210.8	662.3 $\pm$ 629.9	315.9 $\pm$ 210.8	662.3 $\pm$ 629.9	1.87 (1.12, 3.11)	
t _{max} (h)†	4 (4–4)†	1.5 (1.5–4)†		3 (1.5–8)†	3 (1–4)†		6 (6–6)†	5 (1.5–8)†	6 (6–6)†	5 (1.5–8)†		
t _{1/2} (h)	49.1 $\pm$ 22.4	27.0 $\pm$ 4.21	0.60 (0.43, 0.82)*	32.8 $\pm$ 11.8	17.1 $\pm$ 5.02	0.54 (0.42, 0.69)*	34.5 $\pm$ 11.4	33.1 $\pm$ 27.5	34.5 $\pm$ 11.4	33.1 $\pm$ 27.5	0.82 (0.46, 0.70)	
AUC _{hyd} : AUC _{bup}	8.31 $\pm$ 3.56	17.1 $\pm$ 8.96	1.99 (1.57, 2.55)*	8.11 $\pm$ 5.25	16.0 $\pm$ 5.44	2.15 (1.53, 3.05)*	7.01 $\pm$ 2.31	13.2 $\pm$ 6.07	7.01 $\pm$ 2.31	13.2 $\pm$ 6.07	1.86 (1.36, 2.57)*	

*P < 0.05. †Median (ranges).

Figure 2

Individual values for 4-hydroxybupropion AUC(0 ∞) (A), bupropion AUC(0 ∞) (B) and AUC_{hyd} : AUC_{bup} (C) in 16 healthy subjects after a single oral dose of bupropion before and after daily co-administration with metimazole

hydroxybupropion by 38% (90% CI 26, 48%) before and after metimazole administration. t_{max} values for both bupropion and 4-hydroxybupropion were significantly decreased. AUC_{hyd} : AUC_{bup}, as a measure of CYP2B6 activity, was 7.91 ± 3.90 when bupropion was administered alone and 15.7 ± 6.87 when given with metimazole. Metimazole significantly elevated the AUC ratio of 4-hydroxybupropion : bupropion by 111% (90% CI 75, 133%).

Intra-subject changes in the AUC(0 ∞) for 4-hydroxybupropion, bupropion and AUC_{hyd} : AUC_{bup} are depicted in Figure 2A–C, respectively. It can be seen in Figure 2A and B that only one subject had lower plasma exposure to 4-hydroxybupropion and higher plasma exposure to bupropion after administration of metimazole.

AUC_{hyd} : AUC_{bup} values are shown in Figure 2C with all but one having a higher AUC ratio following use of metamizole.

As shown in Table 1, after metamizole treatment relative to bupropion alone, the GMRs and 90% CI of the AUC(0,∞) ratio of 4-hydroxybupropion : bupropion were 1.99 (1.57, 2.55) for CYP2B6*1/*1 group, 2.15 (1.53, 3.05) for CYP2B6*1/*6 group and 1.86 (1.36, 2.57) for CYP2B6*6/*6 group. The GMRs and 90% CI of the AUC(0,∞) and C_{max} of bupropion were 0.662 (0.521, 0.837) and 0.409 (0.341, 0.490) for CYP2B6*1/*1 group, 0.692 (0.563, 0.851) and 0.401 (0.287, 0.553) for CYP2B6*1/*6 group and 0.752 (0.574, 0.980) and 0.383 (0.318, 0.458) for CYP2B6*6/*6 group. The corresponding values for 4-hydroxybupropion were 1.32 (1.17, 1.48) and 2.54 (1.94, 3.31) for the CYP2B6*1/*1 group, 1.49 (1.18, 1.88) and 2.86 (2.08, 3.94) for the CYP2B6*1/*6 group and 1.40 (1.21, 1.63) and 1.87 (1.12, 3.11) for the CYP2B6*6/*6 group. The *t*_{1/2} value was significantly increased for bupropion and decreased for 4-hydroxybupropion in the CYP2B6*1/*1 and CYP2B6*1/*6 groups. Moreover, the mean percentage changes in pharmacokinetic parameters among the CYP2B6 genotype groups were not significantly different.

Discussion

Consistent with the results of previous studies revealing substantial induction of both expression and activity of CYP2B6 by metamizole treatment, the significantly increased AUC ratios of hydroxylation over bupropion after metamizole use confirmed the inductive effect of metamizole on CYP2B6-catalyzed hydroxylation of bupropion in our study, detected as an average of 2.1-fold higher bupropion hydroxylase activity before and after the use of 1.5 g metamizole day⁻¹ for 4 days. A 1.8-fold increase in the AUC ratio of hydroxybupropion : bupropion after 7 day administration of rifampicin has been previously reported [7], suggesting that metamizole may be comparable with rifampicin as a CYP2B6 inducer, which has also been observed in cultured human hepatocytes [5]. Higher bupropion hydroxylase activity would be expected when metamizole is used more than 4 days.

In the current study, the pharmacokinetic parameters of both bupropion and 4-hydroxybupropion in 16 healthy male subjects were significantly altered by metamizole use and there was a mean 43% increase in the AUC of 4-hydroxybupropion and a mean 31% decrease in the AUC of bupropion. The increased hydroxylation of bupropion with significant reduction in bupropion plasma concentration by metamizole seen in our study may reduce the clinical effects by bupropion since the pharmacological activity of hydroxybupropion is about half that of bupropion [16]. Still, it is uncertain to what degree the efficacy of bupropion may be influenced by metamizole due to the pharmacodynamic variability of bupropion [17, 18].

The *t*_{1/2} value was markedly increased, rather than decreased, for bupropion in the current study. Besides bupropion hydroxylation, there are alternative ketone reduction pathways for bupropion elimination leading to the formation of erythro-hydrobupropion and threo-hydrobupropion which seems not to be mediated by CYP enzymes, and the *t*_{1/2} reported for bupropion does not represent the elimination phase but represents the distribution phase [12, 19]. Therefore, it might be the inhibition of alternative ketone reduction pathways by metamizole that prolongs the *t*_{1/2} of bupropion.

Metamizole also seems to induce hydroxybupropion elimination by resulting in a shorter apparent terminal *t*_{1/2} of 4-hydroxybupropion. As suggested by the previous study [5], the chemical structures of metamizole and its derivatives are similar to that of phenobarbital, which activates the nuclear receptor constitutive androstane receptor (CAR) in an indirect manner. Hydroxybupropion can undergo phase II metabolism primarily via glucuronidation [19]. UDP-glucuronosyltransferase is one of the targets of CAR [20]. Therefore, it is supposed that metamizole might induce the further metabolism of 4-hydroxybupropion by inducing UDP-glucuronosyltransferase through activating CAR. Further explorations should be made to confirm this consumption.

The individuals with CYP2B6*6 alleles with lower basal bupropion hydroxylase activity exhibited a similar extent of induction for bupropion hydroxylation by metamizole compared with wild-type, indicating that the mutant genotypes did not interfere with inducibility of bupropion hydroxylation by metamizole, which agree with *in vitro* study findings [5]. The mean percentage changes in pharmacokinetic parameters among the CYP2B6 genotype groups were not significantly different. Except for the relative small number of individuals, genetic polymorphisms of other genes such as NR1I2 are involved in the possible mechanism [21].

There are several limitations in our study. Females not using hormonal contraception should have been enrolled. The pharmacokinetics of bupropion and its metabolite should be examined after 24 h of dosing and then later into therapy to see if metamizole is both an activator of CYP2B6 and an inducer. Sterospecific assays for bupropion would be helpful for clarifying the potential mechanisms of the effects of metamizole.

Our study is the first preliminary work to demonstrate substantial induction of CYP2B6-catalyzed bupropion hydroxylation by metamizole in humans, and the extent of induction may be clinically significant for patients being co-administered metamizole and bupropion. Plasma concentrations and thus therapeutic efficacy of other CYP2B6 substrates including methadone, cyclophosphamide, ifosfamide, propofol, efavirenz, ketamine, tamoxifen, sertraline and meperidine may be altered by metamizole. Whether interactions between these agents and metamizole are clinically significant deserve further investigation.

Competing Interests

None of the authors has any conflict of interest regarding this study.

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