Effects of high-fat diet and CYP2B6 mutants on the pharmacokinetics of bupropion and hydroxybupropion among healthy chinese subjects

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Abstract

Aims To provide evidence for the clinically rational administration of bupropion (BUP), the effects of high-fat diet and CYP2B6 mutants on BUP and hydroxybupropion (HBUP) among 44 healthy Chinese subjects. Methods The concentrations of BUP and HBUP in plasma were determined with a high performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) analysis. Genotypes were ascertained after amplified by polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP). Results The maximum plasma concentration (Cmax) and time to Cmax (tmax) of BUP as well as the concentration–time curve (AUC(0-96)) and Cmax of HBUP all increased by 1.18-, 1.41-, 1.38-, and 1.33-fold in the feeding group relative to the fasting group, respectively. Interestingly, the Cmax and terminal half-life (t1/2) of BUP increased by 1.33- and 1.39-fold among those subjects carrying the CYP2B6*1/*1 genotype in the feeding group relative to those in the fasting group. Similarly, the apparent volume of distribution (Vd) and clearance (CL) of HBUP increased by 1.38- and 1.59-fold, respectively, while the Cmax and AUC(0-96) of HBUP decreased by 1.44- and 1.49-fold among those subjects carrying the CYP2B6*1/*1 genotype in the feeding group relative to those in the fasting group. Concliusion These data suggest that high-fat diet and CYP2B6 mutants can influence the pharmacokinetic parameters of BUP and HBUP, thereby offering clear evidence for the rational administration of BUP among Chinese subjects in clinical settings.

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Abstract

Aims

To provide evidence for the clinically rational administration of bupropion (BUP), the effects of high-fat diet and *CYP2B6* mutants on BUP and hydroxybupropion (HBUP) among 44 healthy Chinese subjects.

Methods

The concentrations of BUP and HBUP in plasma were determined with a high performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) analysis. Genotypes were ascertained after amplified by polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP).

Results

The maximum plasma concentration (C_{max}) and time to C_{max} (t_{max}) of BUP as well as the concentration–time curve (AUC(0-96)) and Cmax of HBUP all increased by 1.18-, 1.41-, 1.38-, and 1.33-fold in the feeding group relative to the fasting group, respectively. Interestingly, the Cmax and terminal half-life ($t_{1/2}$) of BUP increased by 1.33- and 1.39-fold among those subjects carrying the *CYP2B6*1/*1* genotype in the feeding group relative to those in the fasting group. Similarly, the apparent volume of distribution (Vd) and clearance (CL) of HBUP increased by 1.38- and 1.59-fold, respectively, while the Cmax and AUC(0-96) of HBUP decreased by 1.44- and 1.49-fold among those subjects carrying the *CYP2B6*1/*1* genotype in the feeding group relative to those in the fasting group. However, no statistically significant difference among these pharmacokinetic parameters was detected for those subjects carrying a *CYP2B6* mutant with the exception of the tmax of BUP, which showed a 1.61-fold increase among the feeding *CYP2B6* mutant subjects relative to the fasting subjects.

Concliusion

These data suggest that high-fat diet and *CYP2B6* mutants can influence the pharmacokinetic parameters of BUP and HBUP, thereby offering clear evidence for the rational administration of BUP among Chinese subjects in clinical settings.

Keywords: high-fat diet, fasting and feeding, *CYP2B6* mutants, pharmacokinetics, bupropion, hydroxybupropion

1 What is already known about this subject

The inductive or inhibitive effects on *CYP2B6* activity as reflected by BUP hydroxylation have been extensively studied.

2 What this study adds

No study has examined the effects of a combination of high-fat diet and *CYP2B6* genotypes on the pharmacokinetics of BUP and HBUP among Chinese subjects.

The maximum plasma concentration and absorptive extent of BUP were enhanced by the intake of high-fat breakfast. The maximum absorption time of BUP was delayed and the speed of absorption was lower in the feeding condition than in the fasting condition.

Under the same feeding condition, the absorption of BUP and metabolism of HBUP were not influenced in the *CYP2B6*1/*1* and *CYP2B6* mutants. For the same genotypes, the pharmacokinetic parameters of *CYP2B6*1/*1* subjects were obviously affected by high-fat diet, while those of *CYP2B6* mutants showed the opposite trend.

1 INTRODUCTION

Bupropion (BUP) is an effective nor-epinephrine and dopamine uptake inhibitor that is often used for inhibiting depression and smoking behavior. This drug can be metabolized into three major metabolites (Fig.1), namely, hydroxybupropion (HBUP), threohydrobupropion (TBUP), and erythrohydrobupropion (EBUP)[1,2]. Among these metabolites, HBUP is identified as the primary active metabolite for curbing depression and smoking behavior among humans[3]. BUP is also metabolized by the CYP3A4 system into either TBUP or EBUP, but their contents are limited[4]. CYP2B6 is the most effective enzyme in the second subgroup of cytochrome P450 and its genes are prone to mutation[5,6]. The predominant haplotypes

associated with BUP mediation include allele*4, allele*6, and allele*9 in *CYP2B6* . The *A785G* and *G516T* variants exist in allele*4 and allele*9, respectively, and both exist in allele*6[7].

The inductive or inhibitive effects on CYP2B6 activity as reflected by BUP hydroxylation have been extensively studied[8, 9]. Both *in vivo* and *in vitro* studies have shown that allele*4 is related to a higher catalytic activity, which, in turn, accelerates the transformation of BUP into HBUP[2]. Compared with wild-type *CYP2B6*1* variants, *CYP2B6*4* variants increase the catalytic activity of CYP2B6 and the BUP clearance[10]. Consistent with the results of previous studies, the homozygous and heterozygous *CYP2B6*6* have a lower HBUP concentration compared with their wild-type variants[2, 11].

Other studies have established a strong correlation between allele*6 variants and the BUP clearance or HBUP plasma levels[7,11]. *CYP2B6*6* alleles and their wild-type variants show a similar extent of induction for bupropion hydroxylation by metamizole[12]. The presence of *CYP2B6*6* decreased the function of CYP2B6 and consequently increased the plasma BUP concentration in allele*6 variants relative to the wild-type variants, but the opposite trend was observed for HBUP concentration[2]. Increasing the frequency of *G516T* polymorphism would enable allele*9 to reduce the enzymatic function and enhance the plasma BUP concentration[13]. However, no study has examined the effects of a combination of feeding and *CYP2B6* genotypes on the pharmacokinetics of BUP and HBUP among Chinese subjects. Therefore, this study aimed to investigate the effects of high-fat diet and *CYP2B6* mutants on the pharmacokinetics of BUP and HBUP among Chinese subjects.

2 METHODS

2.1 Subjects

The fasting and feeding study protocols were approved by the ethics committee of the General Hospital of Ningxia Medical University, Yinchuan, Ningxia, China and the written informed consents were obtained from the volunteers. The ethics committee's appproval identification number is 2015–133. Forty-four healthy Chinese volunteers were recruited for this study. Subjects were all male, weighted 60-80 kg, aged 18-28 years, and had a normal body mass index range (19-24 kg/m^2) [14]. Drugs, alcohol and caffeine-containing beverages, cigarettes, and nutritional supplements were refrained a week before commencement and throughout the study[15].

2.2 Study protocol[14]

The clinical protocols of fasting and feeding study were designed in a randomized two-process, two-phase, two-sequence, and crossover manner with a 2-week washout period[16,17]. In fasting study without breakfasting on day 1, subjects orally received 150 mg BUP (a tablet of 150 mg BUP SR; Disha, Shandong, China) or 150 mg BUP (a tablet of 150 mg BUP SR; Jingxin, Zhejiang, China) with 200 mL of water at 8:00 am. Then they drank 200 mL of water at 10:00 am, and ingested the meals at 12:00 pm and 18:00 pm. Subjects had no other foods except standard meals applied during the study. On day 15, subjects received another tablet at the same condition. Feeding study was designed as the same as fasting study except the high-fat breakfasting, containing one fried egg, one portion of hash brown potatoes, 220 mL of pure milk, and one drumstick 30 min prior to administration. Serial blood samples (5 ml) were collected using a forearm indwelling venous catheter 1 h prior to dosing and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10, 12, 24, 48, 72 and 96 hour after BUP oral administration[14]. These blood samples were stored in EDTA-K_2 tubes, and then centrifuged at 3000 rpm for 30 min. The separated plasma samples and blood cells were instantly stored at –80° until analysis.

2.3 Concentration assay[14]

The concentrations of BUP and HBUP in plasma were determined[18,19] with a high performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) method[20,21](LC-30A^{TM}, Shimadzu, Kyoto, Japan; API 4000^{TM}, Applied Biosystems, Framingham, MA, USA). A Shimpack XR-ODSIII column (1.6 μm, 50×2.0 mm, Japan) and a mobile phase (acetonitrile:10 mM ammonium formate/ B:A) : 0 min, 5% B;

2.5 min, 30% B; 3.0 min, 30% B; 3.5 min, 5% B; 4.0 min, stop (v/v) at a flow rate of 0.3 mL/min were applied. Venlafaxine was used as the internal standard.

2.4 Calculation of pharmacokinetic parameters

$AUC_{(0\text{-}96)}$, C_{max}, CL, V_d, t_{max} and $t_{1/2}$ of BUP and HBUP of 44 subjects were calculated by non-compartmental method used DAS3.0 software package (Bojia Corp., Shanghai, China). Concentration-time curves and Tables were designed.

2.5 Genotyping of *CYP2B6*

The blood cells were extracted by Blood DNA Kit (50) (e.z.N.A.^{TM}, OMEGA, Norcross, GA, USA) for genomic DNA. *CYP2B6*4* (*A785G*),*CYP2B6*6* (*A785G* , *G516T*) and*CYP2B6*9* (*G516T*) genotypes were ascertained after amplified by polymerase chain reaction (PCR) (Eppendorf AG, Germany) and restriction fragment length polymorphism (RFLP) [14]. The PCR conditions consisted of initial denaturation at 94deg for 5 min, followed by 34 cycles of denaturation at 94deg for 30 s, annealing at 60deg for 40 s for *A785G* and 58deg for *G516T* , and extension at 72deg for 1 min. The final volume of the PCR was 50 uL, including 200 ng of DNA, 10 uM of each primer pair, 2.5 uM of dNTPs, 19 uL of dd H_2O and 25 uL of Taq DNA polymerase (Takara, Dalian, China). Genotype of *A785G* was confirmed by *StyI*(thermo scientific, EU) at 60 overnight, and *G516T* was ascertained by *BsrI* (New England Biolabs, America) at 65deg for 15 min[22].

2.6 Groups among high-fat diet, genotypes and pharmacokinetic parameters

Numbers of fasting and feeding groups were counted. Subjects were grouped into 4 groups by wild type and mutants under fasting and feeding condition. Pharmacokinetic parameters of 44 subjects were grouped based on *CYP2B6* genotypes and feeding condition.*CYP2B6*1/*1* and *CYP2B6*mutants were both contained in fasting and feeding groups. Concentration-time curves were drawn and Tables were tabulated according to categories.

2.7 Statistical analysis

Independent-Sample T and Mann-Whitney U or Kruskal-Wallis tests were used to evaluate $AUC_{(0\text{-}96)}$, C_{max}, CL, V_d, t_{max} and $t_{1/2}$between different groups of BUP and HBUP with 95% confidence intervals (CIs). The results were expressed as the mean +- standard deviation (Mean +- SD) in the Tables and Figures. Statistical results were performed with SPSS (version 22.0, Chicago, IL, USA) for windows. $P<0.05$ was considered statistically significant.

3 RESULTS

3.1 Classification of subjects

All 44 subjects were classified based on fasting, feeding, and*CYP2B6* mutants. Among these subjects, 20 were placed in the fasting group, while 24 were placed in the feeding group. The plasma concentrations of BUP and HBUP were determined via HPLC-MS/MS. The pharmacokinetic parameters were calculated in DAS 3.0 by applying a non-compartmental method.*CYP2B6*4/*6/*9*genotypes and single-nucleotide polymorphism (SNP) were identified by PCR-RFLP. The effects of the genetic polymorphism of *CYP2B6* on BUP were investigated in many studies, but the effects of a combination of feeding and *CYP2B6* genotype on the pharmacokinetics of BUP and HBUP among Chinese subjects have never been examined. Therefore, this study investigated the effects of high-fat diet and *CYP2B6*mutants on the pharmacokinetics of BUP and HBUP among Chinese subjects.

3.2 BUP and HBUP concentrations

The lower limits of quantification for BUP and HBUP were 0.500 ng/mL and 0.600 ng/mL, while the assay ranges used were 0.500 ng/mL–400 ng/mL and 0.600 ng/mL–480 ng/mL, respectively. The mean correlation coefficients for BUP and HBUP were 0.9985 and 0.9960. The intraday and interday precision and accuracy, which were measured by HPLC-MS/MS, were less than +-15%. Our method satisfied the criteria of the

Guidance for Industry Bioanalytical Method Validation (FDA) and the Guideline for Bioanalytical Method Validation (EMA).

Basing on the HPLC-MS/MS conditions in the mentioned concentration assay, BUP, HBUP and venlafaxine are identified and quantified. The structures and full-scan production spectra of the BUP, HBUP and venlafaxine are shown in Fig. 2. The retention time of BUP, HBUP and venlafaxine are 3.32 min, 2.89 min and 3.36 min, respectively. The BUP and HBUP plasma concentrations of the 44 subjects were determined by using the developed method. The concentration–time curve of the subjects in the fasting and feeding groups is shown in Fig. 3. The pharmacokinetic parameters were calculated by using DAS 3.0 and the non-compartmental method, and the results can be seen in Tables 1 and 2.

3.3 Classification of CYP2B6

As shown in Table 3, the genotypes of *CYP2B6*4/*6/*9* were categorized by *516G>T* and *785A>G* mutation, and the numbers of different genotypes are shown in Table 4. The subjects were grouped into the following based on their wild and variant types: fasting *CYP2B6*1/*1* (n=10), feeding *CYP2B6*1/*1* (n=11), fasting *CYP2B6* mutants (n=10), and feeding *CYP2B6* mutants (n=13). The fasting *CYP2B6* mutants contained *CYP2B6*1/*6* , *CYP2B6*1/*4* , *CYP2B6*4/*6* , *CYP2B6*6/*9* , and *CYP2B6*1/*9* genotypes, while the feeding *CYP2B6* mutants contained *CYP2B6*1/*6* , *CYP2B6*1/*4* , *CYP2B6*4/*6* , and *CYP2B6*6/*6* genotypes.

3.4 Pharmacokinetic parameters of BUP and HBUP

The BUP and HBUP plasma concentrations were determined by using the HPLC-MS/MS method. The concentration–time curves of BUP and HBUP differentiated by fasting, feeding, and *CYP2B6* mutants are shown in Figs. 4 and 5. The pharmacokinetic parameters were calculated by using DAS 3.0 and the non-compartmental method, and the results can be seen in Tables 5 to 8. The $AUC_{(0\text{-}96)}$, C_{max}, and T_{max} of BUP and HBUP in fasting *CYP2B6*1/*1* , fasting *CYP2B6* mutants, feeding *CYP2B6*1/*1* , and feeding *CYP2B6* mutants can be seen in Figs. 4 and 5.

4 DISCUSSION

The canagliflozin/metformin FDC tablet was recommended to be taken with meals to reduce the symptoms of gastrointestinal intolerability associated with metformin[23]. The variations in the rate of clarithromycin-extended release absorption were higher in the feeding condition-in which the tablets resided longer in the stomach-than in the fasting condition among healthy Jordanian men[24]. Diclofenac potassium oral solution and tablet formulations produced statistically and significantly different C_{max} and t_{max} yet similar AUC under both feeding and fasting conditions. The feeding condition produced a significantly lower C_{max} for both formulations and profoundly delayed the t_{max} for the tablet but did not influence the t_{max} for the solution formulation[25]. No spikes were observed in the plasma concentration versus time profiles up to median t_{max} or beyond. Therefore, we found no evidence to support the dose dumping of the test formulation in either the fasting or feeding conditions. No bioequivalence limits were set for percentage of AUCE (AUCINF_pred due to extrapolation from Tlast to infinity), but the application of standard BE (Bioequivalence) limits of 80% to 125% suggested that the feeding study was clearly underpowered given the high WSV (withjn—subjectvariability) at the early time points[15]. Pantoprazole might not be a highly variable drug product when co-administered with high-fat diet at a single oral dose[26]. The administration of canagliflozin with a high-fat meal also had no effect on the pharmacokinetic parameters, thereby suggesting that canagliflozin tablets may be taken with or without high-fat diet[27]. BUP was allowed to be used as a probe substrate across different sexes and ethnicities as a measure of CYP2B6 activity[28]. The C_{max} and $AUC_{(0\text{-}96)}$ of BUP and HBUP were higher in the feeding condition than in the fasting condition, while the t_{max} of BUP was delayed in feeding condition than in the fasting condition. The maximum plasma concentration and absorptive extent of BUP were enhanced by the intake of high-fat breakfast. The maximum absorption time of BUP was delayed and the speed of absorption was lower in the feeding condition than in the fasting condition. The effects of BUP on treatment were increased by the high plasma concentration.

Tables 1 and 2 showed that the C_{max} and t_{max} of BUP as well as the $AUC_{(0-96)}$ and C_{max} of HBUP increased by 1.18-, 1.41-, 1.38-, and 1.33-fold in the feeding group relative to the fasting group, respectively ($P<0.05$). Both high-fat diet and *CYP2B6* mutants influenced the pharmacokinetic parameters of BUP and HBUP among the Chinese subjects.

The *CYP2B6* mutants also influenced the pharmacokinetic parameters. Specifically, the C_{max} and $t_{1/2}$ of BUP increased by 1.33- and 1.39-fold among those subjects carrying a *CYP2B6*1/*1* genotype in the feeding group relative to the fasting group, respectively ($P<0.05$). Similarly, the V_d and *CL* of HBUP increased by 1.38- and 1.59-fold, but the C_{max} and $AUC_{(0-96)}$ of HBUP decreased by 1.44- and 1.49-fold among those subjects carrying a *CYP2B6*1/*1* genotype in the feeding group relative to the fasting group, respectively ($P<0.05$). However, no statistical difference among the aforementioned parameters was detected for those subjects carrying a *CYP2B6* mutant with the exception of the t_{max} of BUP, which increased by 1.61-fold among the feeding *CYP2B6* mutant subjects compared with the fasting subjects ($P<0.05$). The pharmacokinetic parameters of BUP and HBUP in fasting *CYP2B6*1/*1* and fasting *CYP2B6* mutants are shown in Table 5. The $AUC_{(0-96)}$, C_{max}, *CL* , V_d, t_{max}, and $t_{1/2}$ of BUP and HBUP in fasting wild-type were the same as those in the fasting *CYP2B6* mutants. The feeding wild-type and feeding *CYP2B6* mutants demonstrated the same trends as shown in Table 6. Table 7 shows that the $AUC_{(0-96)}$ and C_{max} of BUP and HBUP in the feeding wild-type were higher than those in the fasting wild-type. Moreover, the *CL* and V_d of HBUP in the feeding wild-type were less than those in the fasting wild-type ($P<0.05$). As shown in Table 8, the $AUC_{(0-96)}$ and C_{max} of BUP and HBUP increased in the feeding *CYP2B6* mutants than in the fasting *CYP2B6* mutants. By contrast, the *CL* and V_d of BUP decreased in the feeding *CYP2B6* mutants and did not reach statistical significance in the fasting *CYP2B6* mutants. Under the same feeding condition, the absorption of BUP and metabolism of HBUP were not influenced in the *CYP2B6*1/*1* and *CYP2B6* mutants. For the same genotypes, the pharmacokinetic parameters of *CYP2B6*1/*1* subjects were obviously affected by high-fat diet, while those of *CYP2B6* mutants showed the opposite trend. Therefore, BUP should be administered among Chinese subjects carrying *CYP2B6*1/*1* after their high-fat food intake in order to improve the effects of the clinical treatments of BUP. Moreover, BUP can be administered among Chinese subjects with *CYP2B6* mutants in either fasting or feeding conditions.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

All authors performed experiments. Hong Wan Dang and Xiao Ying Yang designed the study; Shi Jie Wei, Yan Ni and Hao Zhang contributed new reagents or analytic tools; Wen Ping Zhang, Yu Xin Zhang and Hui Ma analyzed data and prepared the manuscript.

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Table 1: Pharmacokinetic parameters (Mean+-SD) of BUP in fasting and feeding groups.

BUP PK	$t_{1/2}$ **(h)**	t_{max} **(h)**	V_d **(L/ng)**	CL **(mL/h*ng)**	C_{max} **(ng/mL)**	$AUC_{(0-96)}$ **(h*ng/**
Fasting group (n=20)	13.07±4.16	2.30±0.80	3.877±0.962	214.13±53.84	79.75±19.21	730.74±167.51
Feeding group (n=24)	15.27±4.75	3.25±1.33	4.091±1.554	187.97±40.60	94.11±22.23	817.16±162.78
P	0.114	0.021*	0.595	0.073	0.029*	0.091

*P < 0.05 was statistically significant; PK = pharmacokinetic; p = Feeding group *vs* . Fasting group

Table 2: Pharmacokinetic parameters (Mean±SD) of HBUP in fasting and feeding groups.

HBUP PK	$t_{1/2}$ **(h)**	t_{max} **(h)**	V_d **(L/ng)**	CL **(mL/h*ng)**	C_{max} **(ng/mL)**	$AUC_{(0-96)}$ **(h*ng/**
Fasting group (n=20)	21.64±4.60	6.45±1.70	0.887±0.221	29.60±9.55	130.05±41.55	5311.82±1865.48
Feeding group (n=24)	22.02±3.63	6.65±2.40	0.757±0.412	24.80±16.06	172.56±80.77	7325.03±3309.23
P	0.760	0.923	0.214	0.248	0.020*	0.020*

*P < 0.05 was statistically significant

Table 3: Genotyping of*CYP2B6*4/*6/*9.

Genotyping	785AA	785AG	785GG
516GG	*1/*1	*1/*4	*4/*4
516GT	*1/*9	*1/*6	*4/*6
516TT	*9/*9	*6/*9	*6/*6

Table 4: Numbers of subjects with *CYP2B6* genotypes.

Genotypes		**Fasting group (n=20)**	**Feeding group (n=24)**
*CYP2B6*1/*1*	*CYP2B6*1/*1*	n=10	n=11

CYP2B6 mutants	*CYP2B6*1/*6*	n=3	n=7
	*CYP2B6*1/*4*	n=2	n=2
	*CYP2B6*4/*6*	n=1	n=3
	*CYP2B6*6/*9*	n=3	n=0
	*CYP2B6*6/*6*	n=0	n=1
	*CYP2B6*1/*9*	n=1	n=0

Table 5: Pharmacokinetic parameters (Mean±SD) of BUP and HBUP in fasting *CYP2B6*1/*1* and fasting mutants groups.

	$t_{1/2}$ (h)	t_{max} (h)	V_d (L/ng)	CL (mL/h*ng)	C_{max} (ng/mL)	$AUC_{(0-}$
BUP PK						
Fasting *CYP2B6*1/*1* (n=10)	11.51±3.69	2.40±0.97	3.501±0.752	219.46±54.05	74.58±19.65	716.99±
Fasting *CYP2B6* mutants (n=10)	14.64±4.18	2.20±0.63	4.254±1.035	208.79±55.99	84.92±18.26	744.48±
P	0.093	0.591	0.079	0.670	0.239	0.724
HBUP PK						
Fasting *CYP2B6*1/*1* (n=10)	19.75±3.79	6.30±1.70	0.830±0.140	30.64±10.08	125.64±24.74	5081.26
Fasting *CYP2B6* mutants (n=10)	23.53±4.73	6.60±1.78	0.943±0.277	28.54±9.41	134.45±54.68	5542.37
P	0.064	0.704	0.265	0.637	0.648	0.594

*P < 0.05 was statistically significant; PK = pharmacokinetic

Table 6: Pharmacokinetic parameters (Mean±SD) of BUP and HBUP in feeding *CYP2B6*1/*1* and feeding mutants groups.

	$t_{1/2}$ (h)	t_{max} (h)	V_d (L/ng)	CL (mL/h*ng)	C_{max} (ng/mL)	$AUC_{(0}$
BUP PK						
Feeding *CYP2B6*1/*1* (n=11)	15.95±5.68	2.91±1.41	4.310±2.165	185.16±39.62	98.92±22.62	828.97±
Feeding *CYP2B6* mutants (n=13)	14.69±3.94	3.54±1.23	3.906±0.803	190.34±42.87	90.05±21.95	807.16±
P	0.529	0.256	0.538	0.763	0.341	0.752
HBUP PK						
Feeding *CYP2B6*1/*1* (n=11)	21.89±3.54	6.86±2.61	0.601±0.105	19.30±3.72	180.82±38.68	7555.68
Feeding *CYP2B6* mutants (n=13)	22.14±3.84	6.46±2.29	0.889±0.525	29.45±20.78	165.57±105.56	7129.85
P	0.870	0.692	0.087	0.434	0.155	0.311

*P < 0.05 was statistically significant; PK = pharmacokinetic

Table 7: Pharmacokinetic parameters (Mean±SD) of BUP and HBUP in fasting *CYP2B6*1/*1* and feeding *CYP2B6*1/*1* groups.

	$t_{1/2}$ (h)	t_{max} (h)	V_d (L/ng)	CL (mL/h*ng)	C_{max} (ng/mL)	$AUC_{(0-96)}$
BUP PK						
Fasting *CYP2B6*1/*1* (n=10)	11.51±3.69	2.40±0.97	3.501±0.752	219.46±54.05	74.58±19.65	716.99±18
Feeding *CYP2B6*1/*1* (n=11)	15.95±5.68	2.91±1.41	4.310±2.165	185.16±39.62	98.92±22.62	828.97±17
P	0.049*	0.352	0.277	0.111	0.017*	0.174
HBUP PK						
Fasting *CYP2B6*1/*1* (n=10)	19.75±3.79	6.30±1.70	0.830±0.140	30.64±10.08	125.64±24.74	5081.26±1
Feeding *CYP2B6*1/*1* (n=11)	21.89±3.54	6.86±2.61	0.601±0.105	19.30±3.72	180.82±38.68	7555.68±1
P	0.197	0.773	0.000*	0.002*	0.001*	0.001*

*P < 0.05 was statistically significant; PK = pharmacokinetic

Table 8: Pharmacokinetic parameters (Mean±SD) of BUP and HBUP in fasting *CYP2B6* mutants and feeding *CYP2B6* mutants groups.

	$t_{1/2}$ (h)	t_{max} (h)	V_d (L/ng)	CL (mL/h*ng)	C_{max} (ng/mL)	$AUC_{(0}$
BUP PK						
Fasting *CYP2B6* mutants (n=10)	14.64±4.18	2.20±0.63	4.254±1.035	208.79±55.99	84.92±18.26	744.48±
Feeding *CYP2B6* mutants (n=13)	14.69±3.94	3.54±1.23	3.906±0.803	190.34±42.87	90.05±21.95	807.16±
P	0.975	0.010*	0.374	0.380	0.558	0.351
HBUP PK						
Fasting *CYP2B6* mutants (n=10)	23.53±4.73	6.60±1.78	0.943±0.277	28.5±9.41	134.45±54.68	5542.37
Feeding *CYP2B6* mutants (n=13)	22.14±3.84	6.46±2.29	0.889±0.525	29.45±20.78	165.57±105.56	7129.85
P	0.444	0.876	0.770	0.899	0.407	0.310

*P < 0.05 was statistically significant; PK = pharmacokinetic

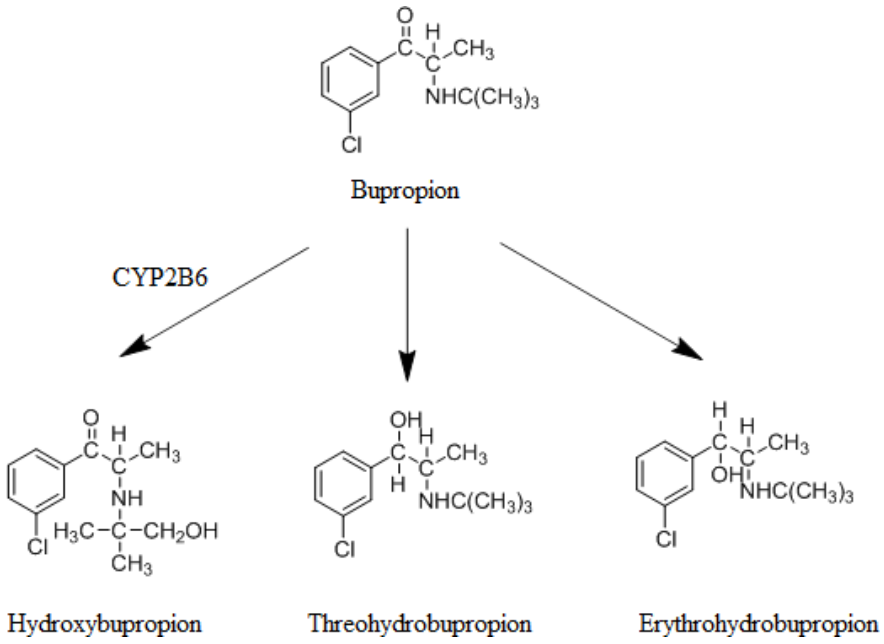

Fig. 1: The chemical structures of bupropion and its major in vivo metabolites: hydroxybupropion, threohydrobupropion and erythrohydrobupropion

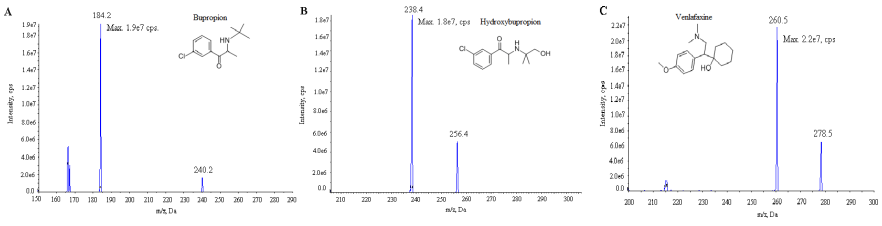

Fig. 2: The structures and full-scan production spectra of the BUP (A), HBUP (B) and venlafaxine (C)

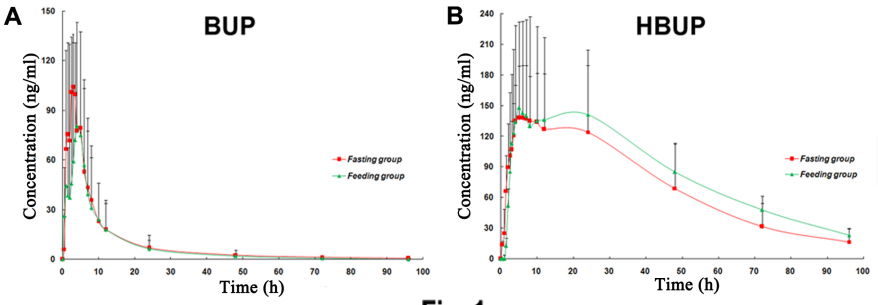

Fig. 1

Fig. 3: Plasma concentration-time curves of BUP and HBUP in fasting and feeding condition after an oral dose of 150 mg BUP in healthy Chinese subject

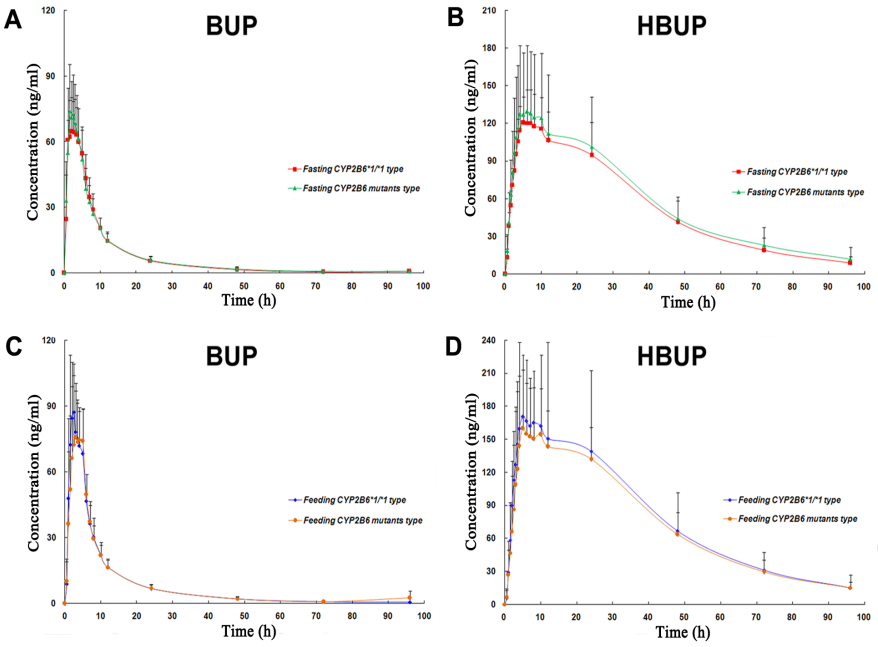

Fig. 2

Fig. 4: Plasma concentration-time curves of BUP and HBUP under the same food condition after an oral dose of 150 mg BUP in Chinese subjects, fasting *CYP2B6*1/*1*group (n=10) compared with fasting *CYP2B6* mutants (n=10), feeding*CYP2B6*1/*1* group (n=11) compared with feeding *CYP2B6* mutants (n=13).

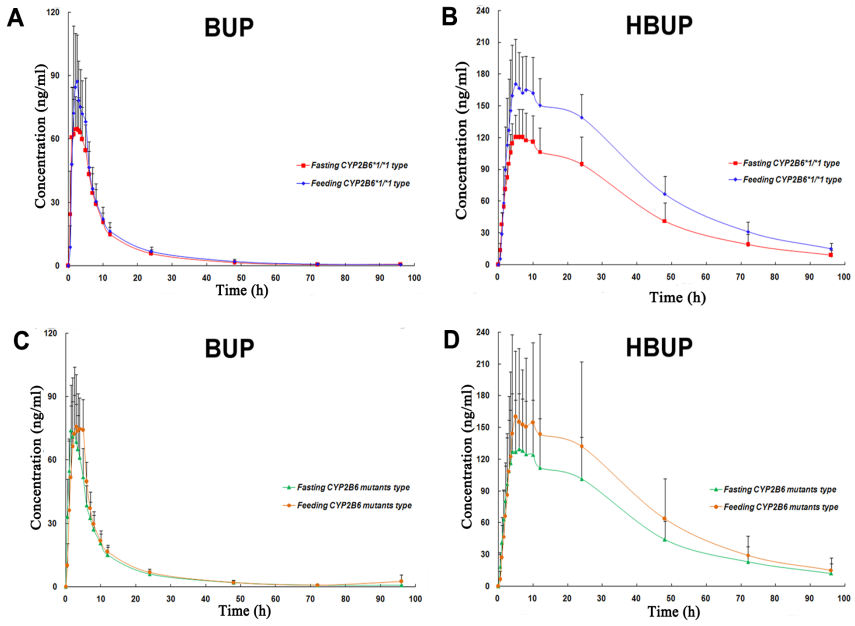

Fig. 3

Fig. 5: Plasma concentration-time curves of BUP and HBUP under different food condition after an oral dose of 150 mg BUP in Chinese subjects, fasting *CYP2B6*1/*1* group (n=10) compared with feeding *CYP2B6*1/*1* group (n=11), fasting *CYP2B6* mutants (n=10) compared with feeding *CYP2B6* mutants (n=13).