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Effects of Genetic Polymorphisms of *CYP2B6* on the Pharmacokinetics of Bupropion and Hydroxybupropion in Healthy Chinese Subjects

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Data Interpretation D
Manuscript Preparation E
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Background: Bupropion (BUP) is an antidepressant and its pharmacological activity is mediated by its major metabolite, hydroxybupropion (HBUP). We investigated the effects of genetic polymorphisms of *CYP2B6* on BUP and HBUP to provide certain evidence on the clinical rational administration of BUP.

Material/Methods: Plasma BUP and HBUP concentrations were assayed using high performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS).

Results: A total of 23 healthy volunteers (eleven participants with *CYP2B6*1/*1*, 7 participants with *CYP2B6*1/*6*, 3 participants with *CYP2B6*4/*6*, and 2 participants with *CYP2B6*1/*4*) received orally administered 150 mg of BUP according to protocol. Blood samples were obtained up to 96 hours after administration. The whole blood was subject to genotyping by polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP). The concentration-time curve ($AUC_{(0\rightarrow96)}$), maximum plasma concentration (C_{max}), and terminal half-life ($t_{1/2}$) values of BUP in *CYP2B6*1/*4* were lower than those of *CYP2B6*1/*1*. By contrast, the time to C_{max} (t_{max}) value of the former was higher than that of the latter. The HBUP $AUC_{(0\rightarrow96)}$ values in *CYP2B6*4/*6* and *CYP2B6*1/*4* increased to values 1.12-fold and 1.98-fold, compared with *CYP2B6*1/*1* carriers. However, the HBUP $AUC_{(0\rightarrow96)}$ value in *CYP2B6*1/*1* was 1.51-fold higher than that in *CYP2B6*1/*6*. Similarly, the HBUP C_{max} values in *CYP2B6*4/*6* and *CYP2B6*1/*4* increased by 1.12-fold and 1.97-fold, whereas the HBUP C_{max} value in *CYP2B6*1/*6* decreased to a value 1.64-fold lower than that in *CYP2B6*1/*1*.

Conclusions: Genetic polymorphisms of *CYP2B6* influence the pharmacokinetic parameters of BUP and HBUP and thus establish rational BUP administration for Chinese patients in clinical settings.

MeSH Keywords: **Clinical Trial, Phase I • Pharmacokinetics • Polymorphism, Single Nucleotide**

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Background

Depression is a major psychiatric disorder and may significantly lower the quality of life and increase the burden of distress [1,2]. Depressive symptoms have a prevalence rate of 20–64% among patients in hospitals and 15–45% among elderly people with medical problems [3,4]. At present, effective drugs that can cure depression remain unavailable.

Bupropion (BUP) is a smoking cessation and antidepressant drug and functions as an effective norepinephrine and dopamine uptake inhibitor. BUP is metabolized to 3 major metabolites, namely, hydroxybupropion (HBUP), threohydrobupropion (TBUP), and erythrohydrobupropion (EBUP) [5,6]. BUP is also used for treating Parkinson disease, and it is metabolized primarily by CYP2B6 [7]. However, the metabolic mechanisms of BUP are currently unclear. Meanwhile, HBUP is the primary active metabolite for smoking cessation and anti-depression in humans.

The CYP3A4 system metabolizes BUP into either TBUP or EBUP, albeit at limited quantities [8]. CYP2B6 is the most effective enzyme in the second subgroup of cytochrome P450, but its genes are prone to mutation [9]. The predominant haplotypes associated with BUP mediation are allele*4, allele*6, and allele*9 in *CYP2B6*. The *A785G* variant exists in allele*4; the *G516T* variant occurs on allele*9; and allele*6 consists of *A785G* and *G516T* variants [10].

Induction or inhibition of CYP2B6 activity reflected by BUP hydroxylation were extensively investigated in previous studies [11,12]. Both *in vivo* and *in vitro* studies showed that allele*4 relates to increased catalytic activity and accelerates the transformation of BUP into HBUP [6]. Meanwhile, *CYP2B6*4* variants raise the catalytic activity of CYP2B6 and increase the BUP clearance to greater extent than wild-type allele *CYP2B6*1* [13]. The presence of homozygous and heterozygous *CYP2B6*6* results in HBUP concentrations is lower than those observed in the presence of its wild-type allele [6,14]. Moreover, other studies establish a strong correlation between allele*6 variants and BUP clearance or plasma HBUP levels [10,14]. A similar extent of induction for BUP hydroxylation by metamizole occurs in *CYP2B6*6* alleles [15]. Reduced CYP2B6 function is observed in the presence of *CYP2B6*6*, this reduction results in decreased HBUP concentration and higher elevated plasma BUP concentration in allele*6 variants compared with that in the wild-type allele [6]. At high *G516T* polymorphism frequencies, allele*9 exhibits low enzymatic function [16]. Meanwhile, *CYP2B6* polymorphisms that influence BUP and HBUP metabolism and effects remains unknown.

In the present study, the effects of the genetic polymorphisms of *CYP2B6* on the pharmacokinetics of BUP and HBUP among healthy Chinese participants was investigated to provide a strong evidence that supports the rationality of BUP administration to healthy Chinese patients.

Material and Methods

Ethic statement

Written informed consents were obtained from the volunteers. The study protocol was approved by the Ethics Committee of the General Hospital of Ningxia Medical University, Yinchuan, Ningxia, China.

Study participants

A total of 23 healthy Chinese participants from Ningxia enrolled in the Phase I clinical trial who were successfully genotyped with specific *CYP2B6* genotypes (11 participants with *CYP2B6*1/*1*, 7 participants with *CYP2B6*1/*6*, 3 participants with *CYP2B6*4/*6*, and 2 participants with *CYP2B6*1/*4*) were enrolled in this study. Study participants were ascertained as healthy and without disease history during physical examinations. Participants also abstained from drugs, alcohol, caffeine-containing beverages, cigarettes, and nutritional supplements for 2 weeks before study commencement and throughout the study [17]. Participants were male, aged 18–28 years, weighed 60–80 kg, and had a normal body mass index range (19–24 kg/m^2). Hongwan Dang and Xiaoying Yang together created the study group according to selection criteria.

Study design

The clinical protocol was designed in a 2-process, 2-phase, 2-sequence, randomized, and crossover manner over a 2-week washout period between phases [18,19]. After overnight fasting and on day 1, from 6: 00 am to 8: 00 am, the participants could not have any food or water, then 150 mg of BUP (a tablet of 150 mg of BUP SR; Disha, Shandong, or Jingxin, Zhejiang) was orally administrated with 200 mL of water at 8: 00 am. Each participant drank 200 mL of water at 10: 00 am, ingested meals at 12: 00 pm and at 18: 00 pm and drank water freely after 12: 00 pm. On day 15, the participants changed to administration of another tablet at concordant conditions. Participants had no other food except the standard meals given during the study.

Blood sampling

Serial blood samples (5 mL) were collected with a forearm indwelling venous catheter 1 hour 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 hours after BUP administration. Blood samples were stored in EDTA-K_2 tubes, and centrifuged (3000 rpm, 5 min) within 0.5 hours. The

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separated plasma samples and blood cells were immediately stored at -80°C until analysis.

Concentration assay

We added 10 µL of venlafaxine (400 ng/mL) to 100 µL of plasma and then mixed this with 300 µL methanol used to precipitate proteins. The mixture was vortexed for 5 min and centrifuged at 14 000 rpm for 10 min at 4°C. Then 200 µL of supernatant was transferred into the autosampler vial for analysis. Plasma BUP and HBUP concentrations were determined [20,21] with high performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) [22,23] (LC-30A™, Shimadzu, Kyoto, Japan; API 4000™, Applied Biosystems, Framingham, MA, USA), equipped with a Shimpack XR-ODSIII column (1.6 µm, 50×2.0 mm, Japan) and programmed mobile phase conditions of (acetonitrile: 10 mM ammonium formate/B: A): at 0 min, 5% B; at 2.5 min, 30% B; at 3.0 min, 30% B; at 3.5 min, 5% B; at 4.0 min, Stop (v/v) at a flow rate of 0.3 mL/min. Venlafaxine was used as internal standard (IS). The subsequent modes of MRM ion transitions were m/z 240.1–184.2 for BUP, m/z 256.1–238.3 for HBUP, and m/z 278.1–260.5 for IS. The $[M+H]^+$ ions were represented by these transitions.

Calculation of pharmacokinetic parameters

Maximum plasma concentration (C_{max}) and time to C_{max} (t_{max}) were obtained from the concentration-time data. The area under the concentration-time curve (*AUC*) showed the extent of BUP absorption or extent of HBUP to which the related CYP450 metabolized BUP. λ_z is the elimination rate constant determined from the terminal slope of the concentration-time plot. The terminal half-life ($t_{1/2}$), which shows the time of half-drug elimination, was calculated as $0.693/\lambda_z$. The parameters of $AUC_{(0\rightarrow 96)}$, C_{max}, t_{max}, and $t_{1/2}$ were calculated through the noncompartmental method in DAS 3.0 software package (Bojia Corp., Shanghai, China). The concentration-time curve and table of 23 participants were calibrated and designed.

Genotyping of *CYP2B6*

The genomic DNA from blood cells was extracted using Blood DNA Kit (50) (e.z.N.A.™, OMEGA, Norcross, GA, USA). *CYP2B6*4* (*A785G*) and *CYP2B6*6* (*A785G*, *G516T*) genotypes were ascertained after amplification by polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP). The PCR conditions consisted of initial denaturation at 95°C for 5 min, followed by 35 cycles of denaturation at 95°C for 30 secs, annealing at 60°C for 40 secs for *A785G* and 58°C for *G516T*, and extension at 72°C for 1 min. Then 50 µL of PCR production was transferred into 1.5 mL EP tube, which contained 200 ng of DNA, 10 µM of each primer pair, 2.5 µM of dNTPs, 19 µL of ddH_2O, and 25 µL of Taq DNA polymerase (Takara, Dalian, China) for amplification at given PCR conditions. The genotypes of *A785G* were confirmed by *Sty*I (Thermo Scientific, EU) at 60°C overnight, and *G516T* were ascertained by *Bsr*I (New England Biolabs, America) at 65°C for 15 min [24].

Genotype and diplotype

The diplotype of *CYP2B6*1/*1* showed *A785A* and *G516G*. *A785G* and *G516T* were the diplotype of *CYP2B6*1/*6*. Genotype of *CYP2B6*1/*6* consisted of *G785G* and *G516T*. *A785G* and *G516G* occurred in *CYP2B6*1/*4* diplotype.

Statistical analysis

One-way ANOVA and Mann-Whitney U or Kruskal-Wallis tests were used to evaluate $AUC_{(0\rightarrow 96)}$, C_{max}, t_{max}, and $t_{1/2}$ between different groups with 95% confidence intervals (CIs). Results were expressed as mean ± standard deviation (mean ±SD) in the table and figure. Statistical results were performed with SPSS (version 22.0, IBM, Armonk, NY, USA) for windows. *P* values below 0.05 were considered statistically significant.

Results

BUP and HBUP concentrations

The lower limits of the quantification for BUP and HBUP were 0.500 and 0.600 ng/mL and the assay ranges used were 0.500–400 ng/mL and 0.600–480 ng/mL, respectively. The mean correlation coefficients for BUP and HBUP were 0.9986 and 0.9961. The accuracy, intra-day and inter-day precision, measured by HPLC-MS/MS, were less than ±15.0%. Our method met the criteria of the Guidance for Industry Bioanalytical Method Validation (FDA) and Guideline on Bioanalytical Method Validation (EMA).

Classification of *CYP2B6*

CYP2B6 genotypes were categorized as *516 G>T* and *785 A>G* mutations. Participants were classified into 4 groups, namely, *CYP2B6*1/*1* (n=11), *CYP2B6*1/*6* (n=7), *CYP2B6*4/*6* (n=3), and *CYP2B6*1/*4* mutants (n=2).

Effects of *CYP2B6* on pharmacokinetic parameters of BUP and HBUP

The relationships between pharmacokinetic properties of BUP and HBUP and genotypes of *CYP2B6* are shown in Figure 1 and Table 1. The pharmacokinetic parameter results of BUP and HBUP depend on *CYP2B6* genotypes-generated differences. The $AUC_{(0\rightarrow 96)}$, $AUC_{(0\rightarrow \infty)}$ and C_{max} of HBUP were significantly different between *CYP2B6*1/*1* and *CYP2B6*1/*6* participants, *CYP2B6*1/*1* and *CYP2B6*1/*4* participants, *CYP2B6*1/*6* and

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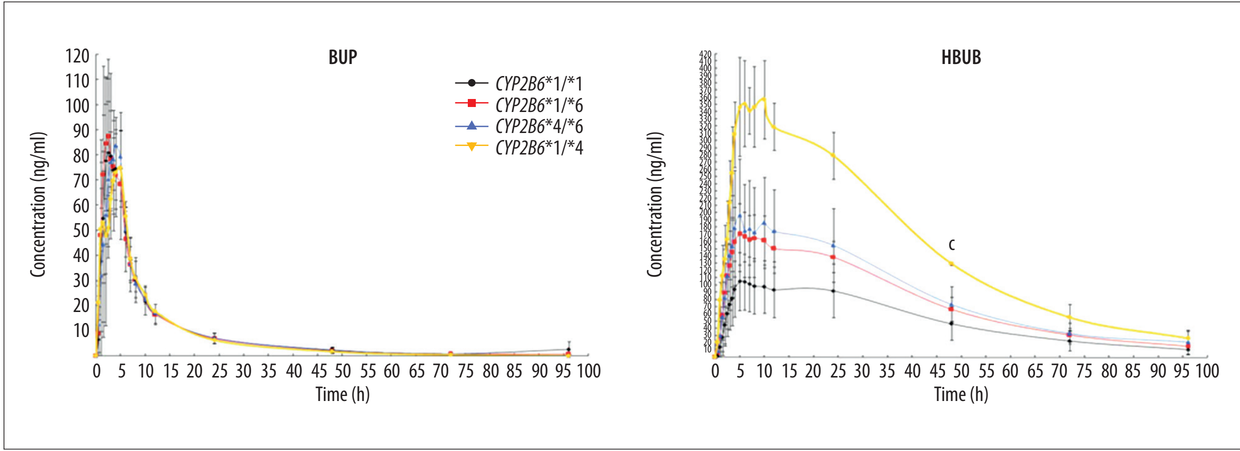

Figure 1. Plasma concentration-time curves of BUP and HBUP after an oral dose of 150 mg BUP in Chinese participants with *CYP2B6*1/*1* (n=11), *CYP2B6*1/*6* (n=7), *CYP2B6*4/*6* (n=3), and *CYP2B6*1/*4* (n=2).

Table 1. Pharmacokinetic parameters (Mean ±SD) of BUP and HBUP in different *CYP2B6* genotypes.

PK parameters	*CYP2B6*1/*1* (n=11)	*CYP2B6*1/*6* (n=7)	*CYP2B6*1/*4* (n=2)	*CYP2B6*4/*6* (n=3)
BUP				
$AUC_{(0\rightarrow\infty)}$ (h*ng/mL)	845.17±180.44	888.08±202.75	786.32±11.83	836.03±91.49
$AUC_{(0\rightarrow 96)}$ (h*ng/mL)	828.97±179.94	847.91±176.16	777.70±4.94	816.45±95.92
C_{max} (ng/mL)	98.92±22.62	96.34±27.77	77.50±4.10	90.43±8.36
$t_{1/2}$ (h)	16.12±5.54	16.87±4.87	12.49±2.98	15.18±2.21
t_{max} (h)	2.91±1.41	3.07±1.40	4.50±0.71	4.17±0.76
HBUP				
$AUC_{(0\rightarrow\infty)}$ (h*ng/mL)	8064.09±1532.87	5385.40±2443.92[a]	15829.18±234.89[ab]	9279.99±3798.31[bc]
$AUC_{(0\rightarrow 96)}$ (h*ng/mL)	7558.96±1400.38	4999.92±2177.85[a]	14996.45±727.05[ab]	8442.65±3069.75[bc]
C_{max} (ng/mL)	180.82±38.68	110.33±41.10[a]	356.50±54.45[ab]	201.67±76.55[bc]
$t_{1/2}$ (h)	22.25±3.41	22.14±4.22	21.13±4.88	23.82±6.81
t_{max} (h)	6.50±2.40	5.71±1.38	6.00±1.41	6.33±3.21

* P<0.05 was statistically significant; PK – pharmacokinetic; [a] *vs. CYP2B6*1/*1*; [b] *vs. CYP2B6*1/*6* and [c] *vs. CYP2B6*1/*4.*

*CYP2B6*4/*6* participants, *CYP2B6*1/*6* and *CYP2B6*1/*4* participants, or *CYP2B6*4/*6* and *CYP2B6*1/*4* participants (all *P* values were below 0.05). The pharmacokinetic parameters of BUP among the 4 groups did not reach statistical difference. $AUC_{(0\rightarrow 96)}$, C_{max} and $t_{1/2}$ of BUP in *CYP2B6*1/*4* carriers were lower than *CYP2B6*1/*1* carriers, whereas t_{max} was higher. Moreover, $AUC_{(0\rightarrow 96)}$ of HBUP in *CYP2B6*4/*6* and *CYP2B6*1/*4* carriers increased by 1.12-fold and 1.98-fold compared with *CYP2B6*1/*1* carriers, respectively. Similarly, C_{max} of HBUP in *CYP2B6*4/*6* and *CYP2B6*1/*4* carriers increased 1.12-fold and 1.97-fold compared with *CYP2B6*1/*1* carriers. Meanwhile, $AUC_{(0\rightarrow 96)}$ of HBUP in *CYP2B6*1/*1* carriers was 1.51-fold higher than that in *CYP2B6*1/*6* carriers. C_{max} of HBUP in *CYP2B6*1/*6* carriers was decreased by 1.64-fold over *CYP2B6*1/*1* carriers. However, the difference between t_{max} and $t_{1/2}$ of participants carrying *CYP2B6*4/*6* genotypes was nonsignificant.

Discussion

In this study, plasma concentrations of BUP and HBUP were determined by HPLC-MS/MS, and pharmacokinetic parameters were calculated by noncompartmental method using Phoenix WinNonlin 6.3 and DAS 3.0 software package. *CYP2B6* variants and SNPs were identified through a combination of PCR and RFLP. We found that pharmacokinetic parameters of BUP and HBUP was greatly influenced by *CYP2B6* genetic polymorphisms among healthy Chinese study participants.

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A rapid and sensitive method was applied for determination of BUP and HBUP in human plasma by HPLC-MS/MS based on previously published protocols [22,25]. The linear curves of BUP and HBUP in the plasma samples ranged from 0.500 ng/mL to 400 ng/mL and from 0.600 ng/mL to 480 ng/mL, respectively. HPLC-MS/MS is a reliable and robust method for BUP and HBUP analysis compared with UV detection. Meanwhile, the method of RFLP was employed restriction endonucleases to digest target specific DNA sequences [27,28] exhibiting high discriminatory power, low complexity, and high capacity in differentiating isolated geographical areas [29]. Mutations in the target site also tested positive in PCR-RFLP [30]. Amplification conditions were optimized through PCR, and the presence of PCR products was confirmed through RFLP. Through RFLP, we were able to distinctly distinguish the bands of *G516T* and *A785G*, and accurately compare different genotypes. Furthermore, PCR-RFLP enabled us to verify the mutants we selected and analyze the exact relation between pharmacokinetics and genotypes.

The concentrations and metabolism of BUP and HBUP in plasma was affected by *CYP2B6* genetic polymorphisms. The *CYP2B6* gene is highly polymorphic [31], with 38 numerous allele variants [32]. Consistent with the results of previous study, *CYP2B6*1/*1* and *CYP2B6*1/*6* carriers were extensive metabolizers (EMs), and intermediate metabolizers (IMs), respectively [22]. *CYP2B6*1/*4* was an ultra-rapid metabolizer (UMs) of BUP and thus extensively induced BUP hydroxylation [6]. In the present study, the *CYP2B6*1/*6* allele carriers showed high BUP concentration and slow elimination, while *CYP2B6*1/*4* carriers exhibited low BUP concentration and fast elimination. In addition, *CYP2B6*4/*6* did not alter BUP concentration in the same manner as *CYP2B6*1/*1*. Overall, the pharmacogenetic data of *CYP2B6* on BUP and HBUP concentrations indicated that catalytic diversities possibly existed in different *CYP2B6* genotypes. The low hepatic expressions of c.516G>T and c.785A>G SNPs observed in BUP reflected variable activities. Meanwhile, SNPs at positions 516 and 785 on the *CYP2B6* gene are essential in the metabolism of several drugs [33,34]. *CYP2B6* T516T was definitely related to plasma concentration, supporting its effect on lower pharmacokinetic parameters of BUP [33]. Although high plasma BUP levels were observed in *CYP2B6*9* participants at all time-points, they were all well-tolerated within the therapeutic window and had no adverse effects. The functional impacts of *CYP2B6* A785G are associated with the enhanced catalytic activation of hydroxylation [34], exhibiting rapidly metabolic activity. *CYP2B6* catalyzed the hydroxylation of a diverse number of xenobiotics, and the metabolic activity in hydroxylation relied on SNPs [35]. Nevertheless, *CYP2B6* pharmacogenomics is not fully explored with respect to the combined effects of several gene variants on metabolism and catalytic properties [31].

The pharmacokinetic properties varied according to SNPs with different genotypes. One study found that the $AUC_{(0\rightarrow\infty)}$ and C_{max} values in Indian study participants were found to be higher than those in Chinese study participants [14]. Another study showed that the pharmacokinetic parameters ($AUC_{(0\rightarrow\infty)}$ and C_{max}) of patients from 4 races differed from each other [23]. In our clinical trial, the $AUC_{(0\rightarrow96)}$, $AUC_{(0\rightarrow\infty)}$, C_{max}, t_{max}, and $t_{1/2}$ values of BUP were higher in the *CYP2B6*1/*6* group compared with those in the *CYP2B6*1/*1* group, whereas the same parameters in the *CYP2B6*1/*4* group were significantly lower than those in the *CYP2B6*1/*1* group. Susceptibility to metabolic inhibition reflected the association of *CYP2B6*6* allele with reduced clearance and metabolism [36], validating the metabolism of BUP by *CYP2B6*1/*6* to a moderate degree, such that the $AUC_{(0\rightarrow96)}$, C_{max}, t_{max}, and $t_{1/2}$ of BUP in the *CYP2B6*1/*6* group exceed those in the *CYP2B6*1/*1* group. Concurrently, *CYP2B6*1/*4* accelerated BUP hydroxylation, resulting in lower BUP concentration and content. Despite the accelerated activation in *CYP2B6*1/*4* participants, whose pharmacokinetics of HBUP maintained increasing levels, the BUP and HBUP profiles in *CYP2B6*4/*6* carriers were not different from those in *CYP2B6*1/*1* carriers but significantly differed from those of *CYP2B6*1/*6* or *CYP2B6*1/*4* carriers. Meanwhile, the $AUC_{(0\rightarrow96)}$, $AUC_{(0\rightarrow\infty)}$, and C_{max} values were remarkably different between carriers of *CYP2B6*1/*6* and *CYP2B6*1/*1* or between *CYP2B6*1/*4* and *CYP2B6*1/*1*, indicating the extensive metabolic properties in carriers with *CYP2B6*4/*6* genotype.

Conclusions

The *CYP2B6* alleles influenced metabolic activity by altering the catalytic activity associated with BUP and HBUP. The metabolic mechanisms of BUP and HBUP were associated with *CYP2B6* SNPs, which modify the catalytic properties of mutants versus wild type. When the BUP exposure was within the therapeutic window, the curative effects were directly proportional to the BUP dose. To reach the ideal treatment effects and prevent toxicities, doses of *CYP2B6*1/*4* (UMs), *CYP2B6*1/*6* (IMs), and *CYP2B6*4/*6* (EMs) carriers should be adjusted based on the therapeutic window.

The enzyme functions of CYP2B6 in the mediation of BUP and HBUP among healthy Chinese individuals requires further research. To date, the effects of genetic polymorphisms of *CYP2B6* on the pharmacokinetics of BUP and HBUP in healthy Chinese individuals remains unreported. The *CYP2B6* alleles alter the pharmacokinetic profiles of BUP and HBUP in a dose-dependent manner. Basing on the altered pharmacokinetics of distinctive genotypes, we found that adjusting BUP exposure was necessary to reach the therapeutic window or target concentrations for treatment and prevention of toxic reactions. Thus, when clinicians prescribe BUP to their patients, they should check whether the patients carry UM or EM genotypes (*CYP2B6*1/*4*, *CYP2B6*4/*6,* and *CYP2B6*1/*1*) and IM genotype (*CYP2B6*1/*6*).

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Conflict of interest

None.

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