Abstract

Objective Zuojin Pill has been shown to inhibit the cytochrome P450 (CYP) 2D6 isoenzyme in vitro. In Chinese individuals, CYP 2D6*10 is the most common allele with reduced enzyme activity. In this study, we investigated the pharmacokinetic interaction between Zuojin Pill and the sensitive CYP2D6 probe dextromethorphan in healthy Chinese volunteers with CYP2D6*10 genotype.

Methods A pharmacokinetics interaction study was carried out in three groups with CYP2D6*1/*1 (n = 6), CYP2D6*1/*10 (n = 6), and CYP2D6*10/*10 (n = 6) genotypes. Each participant received a single oral dose of dextromethorphan (15 mg) followed by Zuojin Pill (3 g twice daily) for 7 days, and received 3 g Zuojin Pill with 15 mg dextromethorphan in the last day. Blood samples (0–24 h) and urine samples (0–12 h) were collected at baseline and after the administration of Zuojin Pill, and the samples’ concentration of dextromethorphan and its main metabolite dextrorphan was determined.

Results Compared to baseline values, co-administration of Zuojin Pill (3 g twice daily) for 7 days increased the AUC₀–₂₄ of dextromethorphan [mean (90 % CI)] by 3.00-fold (2.49–3.61) and 1.71-fold (1.42–2.06), and decreased oral clearance (CL/F) by 0.27-fold (0.2-0.40) and 0.57-fold (0.48-0.67) in the participants with CYP2D6*1/*1 and CYP2D6*1/*10 genotypes, respectively. In contrast, no significant change was observed in these pharmacokinetic parameters of the participants with CYP2D6*10/*10 genotype.

Conclusion These data demonstrated that administration of Zuojin Pill inhibited moderately CYP2D6-mediated metabolism of dextromethorphan in healthy volunteers. The inhibitory influence of CYP2D6 was greater in CYP2D6*1/*1 and CYP2D6*1/*10 groups than CYP2D6*10/*10 group.

Keywords CYP2D6*10 genotype · Zuojin Pill · Drug interaction · Dextromethorphan · Pharmacokinetics

Introduction

The use of complementary and alternative medicine has increased in recent years, and, therefore, the associated risks of herb-drug interactions have also increased. The Zuojin Pill (ZJP), which is a traditional Chinese herbal formula and standardized product, contains the herbs Rhizoma Coptidis and Fructus Evodiae in a 6:1 (w/w) ratio. ZJP was first recorded in “Danxi’s Experiential Therapy” for treating gastrointestinal disorders in the fifteenth century. It is officially listed in the Chinese Pharmacopoeia as a prescription for patients suffering from gastric ulcer, gastroesophageal reflux disease, gastritis, and pyloric obstruction, among other disorders [1]. Chemical investigations of ZJP have revealed the presence of six alkaloids: berberine, palmatine, coptisine, jatrorrhizine in Coptis, and evodiamine and rutaecarpine in Evodia [2]. The quantities
of these alkaloids in ZJP are as follows: berberine, 49.6 mg/g; jateorhizine, 7.43 mg/g; palmatine, 7.35 mg/g; coptisine, 4.04 mg/g; evodiamine, 1.42 mg/g; and rutacarpine, 1.26 mg/g [3]. In vitro investigations revealed that ZJP inhibited the cytochrome P450 (CYP) 2D6 isozyme in our study (data not shown), and the two active constituents of ZJP (coptisine and berberine) had potential inhibitory effects on CYP2D6 activity in human liver microsomes [4]. In one study, the IC_{50} values of coptisine and berberine were 4.4 and 49.4 μM, respectively, for CYP2D6 [4], which indicated that an herb-drug interaction could occur when ZJP is concomitantly administered with medications that are metabolized by CYP2D6.

Human cytochrome P450 (CYP) 2D6 is an extensively characterized polymorphic drug-metabolizing enzyme that catalyzes the bio-conversion of many xenobiotics [5, 6]. Approximately 30% of commonly prescribed clinical drugs, including tricyclic antidepressants, selective serotonin reuptake inhibitors, opioids, anti-arrhythmics, antipsychotics, and some beta-blockers, are known to be CYP2D6 substrates [7–9]. CYP2D6 possesses more than 70 significant alleles, which have various catalytic activities [8]. The CYP2D6*10 allele is characterized by a single nucleotide alteration in exon 1 (100C–T) that causes a Pro34Ser amino acid substitution; this change leads to an unstable enzyme with low metabolic activity. The CYP2D6*10 allele has a reported frequency of 51 to 70% in Chinese populations [10].

Previous studies have indicated that a greater magnitude of inhibitory drug–drug interactions occurs in CYP2D6 extensive metabolizers (EMs) than in CYP2D6 poor metabolizers and that the extent of inhibition can be predicted based on the genotypically identified baseline activity of the responsible CYP enzyme [11–13]. Fukuda reported that CYP2D6*10 is less sensitive to inhibition by bufuralol and venlafaxine than CYP2D6*1 [14] and suggested that it is important to investigate the affinity of CYP2D6*10 for different substrates and inhibitors to fully characterize the risks of herb-drug interactions. Thus, for more accurate evaluation of drug interactions, genotyping of drug-metabolizing enzymes, such as CYP2D6, that exhibit clinically significant genetic polymorphisms should be included in drug development programs and the extent of inhibitory drug interactions should be reported according to metabolizer type [15]. The regulatory guidance for drug interaction studies recommends that it is important to identify genetically determined metabolic polymorphisms when evaluating the drug effects on enzymes with polymorphisms, including CYP2D6 [16].

The effect of ZJP on CYP2D6 activity in vivo has not been previously reported. Dextromethorphan (DM) is a sensitive CYP2D6 substrate [16] and is suitable for determining the effect of ZJP on CYP2D6 activity. In this study, we aimed to examine the influence of ZJP on DM pharmacokinetics in healthy Chinese volunteers with the CYP2D6*10 allele. Results of this study will be helpful for optimizing drug dosages and guiding individual therapy with CYP2D6 substrates when ZJP is used at the same time.

Materials and methods

Reagents, materials, and chemicals The ZJP used in this study was manufactured by Hubei Nodse Pharmaceutical Co., Ltd. (China) according to the method established in the Chinese Pharmacopoeia [1]. Dextromethorphan hydrobromide tablets (15 mg/tablet, lot 2009120401) were manufactured by CSPC Ouyi Pharmaceutical Co., Ltd. Dextromethorphan (DM), dextrophan (DEX), and diazepam were purchased from Sigma-Aldrich (USA). HPLC-grade methanol and acetonitrile were purchased from Tedia Company (USA). All other chemicals were of analytical grade. Deionized water was purified using a Milli-Q system (Millipore Corporation, USA).

Study design and participants We conducted a sequential, open-label, two-period trial at the Phase I Drug Clinical Research Ward of Shuguang Hospital. This research was approved by the Medical Ethics Committee of Shuguang Hospital. Written informed consent was obtained from each volunteer before participating in the study. A total of 51 volunteers were screened for CYP2D6 genotype. Of these volunteers, 18 healthy Chinese adults (9 males and 9 females) were recruited to participate in the study. The participants ranged in age from 22 to 26 years, and the body mass indexes of the participants ranged from 19 to 24 kg/m². The participants were classified into three groups on the basis of CYP2D6*10 genotype: CYP2D6*1/*1, CYP2D6*1/*10, and CYP2D6*10/*10. Each study group included three males and three females.

All subjects were determined to be healthy according to medical history, a physical examination, an electrocardiogram, and routine laboratory tests, including complete blood count, blood biochemistry testing, and urinalysis. Smoking and consumption of alcohol, coffee, tea, and any drugs were prohibited during the study period.

Genotyping of CYP2D6*10 Peripheral blood samples were collected and DNA was extracted by total genomic DNA isolation using the Tianamp Blood DNA Kit (Tiangen Biotech Beijing Co., Ltd., China). Three alleles—CYP2D6*1/*1, CYP2D6*1/*10, and CYP2D6*10/*10—were identified using polymerase chain reaction (PCR).

Study procedures and sample collection All of the participants were admitted to the Phase I Drug Clinical Research Ward of Shuguang Hospital on the evening before the day of drug administration. The next morning, after an overnight fast, a single dose of dextromethorphan hydrobromide 15 mg was administered orally to each participant. The subjects were
providing a light standard meal at 4 and 10 h after medication intake. At 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 h after drug administration, a 4-mL blood sample was obtained from the forearm vein of each subject. The blood samples were centrifuged (12,000 rpm for 10 min) at room temperature. The separated plasma samples were stored at −80 °C until analysis. Urine samples were collected before drug administration and during the following intervals after drug administration: 0 to 4 h, 4 to 8 h, and 8 to 12 h. Total urine output was recorded and a 10-mL aliquot of urine was stored at −80 °C until analysis. Beginning on day 2, each subject received ZJP 3 g twice daily for 7 days. On day 8, after an overnight fast, each subject received ZJP 3 g together with dextromethorphan hydrobromide tablets 15 mg. Blood and urine sampling on day 8 followed the same scheme used on day 1.

**Plasma and urine concentrations of DM and DEX** Plasma sample preparation was accomplished by liquid-liquid extraction. Briefly, plasma samples (300 μL) were mixed with 30 μL of 1 mM NaOH solution and 10 μL of internal standard diazepam acetonitrile solution (100 ng/mL), to which 1.5 mL ethyl acetate was added. The samples were centrifuged and the supernatant was removed and then evaporated to dryness under a gentle stream of nitrogen at 55 °C. The residue was reconstituted with 100 μL of mobile phase. After centrifugation at 12,000 rpm for 10 min, the supernatant (10 μL) was directly injected into the liquid chromatography tandem mass spectroscopy (LC-MS/MS) system.

Urine samples (300 μL) were diluted 10 times with mobile phase, and 300 μL of internal standard diazepam acetonitrile solution (10 ng/mL) was added to the sample. The mixture was vortexed for 3 min and centrifuged at 12,000 rpm for 10 min. A 10-μL sample was injected into the LC-MS/MS system.

**Analytical methods** Plasma samples were assayed for DM and urine samples were assayed for DM and DEX using an LC-MS/MS method. The analytes were separated on an Agilent Eclipse XDB-C18 (4.6 mm × 150 mm, 5 μm) with a mixture of 4 mmol·L⁻¹ ammonium acetate and 0.08 % methanoic acid–methanol (30:70, v/v) as the mobile phase at a flow rate of 0.8 mL·min⁻¹. The column oven was maintained at 30 °C. Detection was completed using an API 4000 triple-quadruple mass spectrometer (Applied Biosystems/SCIEX, USA) equipped with an electrospray ionization source operating in the positive ion mode. Quantification was performed using multiple reaction monitoring (MRM) of the transitions of m/z 272.4 → 146.9 for DM, 258.4 → 157.0 for DEX, and 285.2 → 193.1 for diazepam. The collision energy (CE), declustering potential (DP), and collision cell exit potential (CXP) were established as follows: DP, 70 V; CE, 40 V; and CXP, 14.19 V for DM; DP, 76.87 V; CE, 42.77 V; and CXP, 16 V for DEX; and DP 98.06, V; CE, 43 V; and CXP, 12 V for diazepam. This LC-MS/MS assay had been validated over a concentration range of 0.06 to 60 ng/mL according to the US Food and Drug Administration Guidance on Bioanalytical Method Validation. The limit of quantification for both DEX and DM in plasma and urine samples was 0.06 ng/mL, and the coefficients of variation for the interday and intraday assays were less than 15 %. The accuracy, precision, recovery, and stability tests met the requirements for quantitative determination in biological samples.

**Pharmacokinetic and statistical analysis** Pharmacokinetic parameters were calculated by non-compartmental analysis using WinNonlin software (version 5.01, Pharsight Corp., USA). The peak plasma drug concentration (Cₘₐₓ) and time to Cₘₐₓ (Tₘₚₓ) were directly obtained from the plasma concentration–time profile. The elimination rate constant (λz) was calculated from at least three points of the terminal phase of the semi-log regression of the plasma concentration–time curve. The elimination half-life (T₁/₂) was calculated as 0.693/λz. The area under curve from time 0 to infinity (AUCₜ−∞) was estimated as AUCₜ−∞ + Cᵢ / λz, where Cᵢ is the plasma concentration of the last measurable sample and AUCₜ−∞ was calculated according to the linear trapezoidal rule. Total plasma clearance (CL/F) was calculated as dose/AUCₜ−∞. The urinary MR was calculated as (12 h recovery of DM in urine)/(12 h recovery of DEX in urine).

Pharmacokinetic parameters except T₁/₂ and Tₘₚₓ were log-transformed for statistical analysis and the back-transformed for data presentation. The statistical significances of differences among pharmacokinetic parameters of the three genotype groups were tested using one-way analysis of variance, and followed by Dunnett’s method for comparison of parameters between two groups. Tₘₚₓ was analyzed using the Kruskal-Wallis test. A p value less than 0.05 indicated significance. The geometric mean ratios and 90 % confidence intervals (CIs) were calculated for the parameters (Cₘₐₓ, AUC (₀, ₁), AUC (₀, ∞), CL/F, and MR) compared with between the values observed in the CYP2D6*1/*10 (CYP2D6*1/*10 group and those in CYP2D6*1/*1 group or compared with between the values observed at baseline and those after ZJP. Statistical analysis was completed using SPSS software (version 16.0).

On the basis of intra-subject standard deviation of 12 % with respect to the AUCₜ−∞ of dextromethorphan [17], it was calculated that six participants were sufficient to detect a 50 % change in the pharmacokinetic parameters (e.g., AUC and CL/F) of dextromethorphan at a 5 % significance level (α = 0.05) and with 80 % statistical power (β = 0.2), with the use of the t test for paired samples [18, 19].
Results

A total of 51 healthy volunteers were originally screened and the distributions of genotypes were as follows: CYP2D6*1/*1, \( n = 10 \) (20.4 %); CYP2D6*1/*10, \( n = 26 \) (53.1 %); and CYP2D6*10/*10, \( n = 13 \) (26.5 %). Eighteen participants were subsequently enrolled and included in the final analysis of ZJP and drug interactions. The mean (±SD) age of the participants was 24.38 (±1.96) years and the mean body weight was 60.60 (±8.09) kg. There were no statistically significant differences in demographic parameters among the three genotype groups. All 18 participants completed the study with no adverse effects.

The mean plasma concentration–time profiles of dextromethorphan (DM) in subjects with CYP2D6*1/*1, CYP2D6*1/*10, and CYP2D6*10/*10 genotypes in the presence and absence of ZJP are shown in Fig. 1. The pharmacokinetic parameters of DM are presented in Table 1.

At baseline, participants with the CYP2D6*1/*1 genotype had the lowest AUC and \( C_{\text{max}} \) values and participants with the CYP2D6*10/*10 genotype had the highest values (Table 1). The AUC \(_{0-24}\) (mean [90 % CI]) of DM in the CYP2D6*1/*10 and CYP2D6*10/*10 groups were 3.16-fold (2.29–4.03) and 11.99-fold (7.62–16.17), respectively, higher than in the CYP2D6*1/*1 group. The \( C_{\text{max}} \) of DM in the CYP2D6*1/*10 and CYP2D6*10/*10 groups were 3.07-fold (2.29–3.84) and 11.44-fold (6.50–16.38), respectively, higher than in the CYP2D6*1/*1 group. The CL/F of DM in the CYP2D6*1/*10 and CYP2D6*10/*10 groups were 0.26-fold (0.16–0.36) and 0.06-fold (0.04–0.08), respectively, lower than in the CYP2D6*1/*1 group. The MR of DM to DEX (DM/DEX) in the CYP2D6*1/*10 and CYP2D6*10/*10 groups was 2.11-fold (0.77–5.77) and 10.28-fold (3.61–29.26), respectively, higher than in the CYP2D6*1/*1 group.

As shown in Figs. 2 and 3, the MR of DM tended to increase and the oral clearance of DM tended to decrease as the number of variant alleles (CYP2D6*10) increased. This finding indicates a gene-dose effect. The \( t_{1/2} \) of DM in the CYP2D6*10/*10 group was longer than the \( t_{1/2} \) in the CYP2D6*1/*1 and CYP2D6*1/*10 groups, but there were no significant differences in the \( T_{\text{max}} \) of DM among the three groups.

After 1 week of ZJP administration (3 g twice daily), the AUC \(_{0-24}\) of DM increased by 3.00-fold (2.49–3.61) and 1.71-fold (1.42–2.06), and the \( C_{\text{max}} \) of DM increased by 2.60-fold (1.85–3.65) and 1.70-fold (1.30–2.23) in the CYP2D6*1/*1 and CYP2D6*1/*10 groups, respectively, compared to baseline values. Oral clearance decreased by 0.27-fold (0.2–0.40) and 0.57-fold (0.48–0.67) in the CYP2D6*1/*1 and CYP2D6*1/*10 groups, respectively, compared to baseline values. However, after ZJP administration, the 90 % CIs for AUC \(_{0-24}\), \( C_{\text{max}} \) and oral clearance in the CYP2D6*10/*10 group were well inside the established no-effect boundary of 0.80–1.25.

The administration of a 1-week course of ZJP resulted in a 4.87-fold (3.74–6.34) and 2.12-fold (0.94–4.79) increase in the DM/DEX ratio for subjects in the CYP2D6*1/*1 and CYP2D6*1/*10 groups. No significant change was observed in the MR in the CYP2D6*10/*10 group.

Discussion

To our knowledge, this is the first clinical study to demonstrate the effects of ZJP on CYP2D6-mediated metabolism of
dextromethorphan in healthy Chinese volunteers with CYP2D6*10 alleles. The results of this study provide clinically meaningful insight into the magnitude of the effect of ZJP on CYP2D6 activity.

In humans, DM is primarily metabolized by CYP2D6 through O-demethylation into DEX [20]. The formation of DEX from DM provides a reliable measure of CYP2D6 activity in humans, both in vitro and in vivo [21]. There is also minor N-demethylation reaction catalyzed by CYP3A4 to produce 3-methoxymorphinan (3MM) [20]. But we found that ZJP had no significant inhibitory effect on in vivo CYP3A4 activity in healthy volunteer [22]. The decreased oral clearance of DM is attribution to inhibition of CYP2D6.

The MR of DM/DEX concentrations in urine is an in vivo index of CYP2D6 activity [5]. In this study, the mean MRs of DM/DEX were 0.0145, 0.0301, and 0.1387 for the CYP2D6*1/*1, CYP2D6*1/*10, and CYP2D6*10/*10 groups, respectively. None of the participants included in this study were classified as poor metabolizers (PM), according to the cutoff value of the MR of DM/DEX in urine, which was considered to be 0.3 [5]. Therefore, in this study, the 12 participants with CYP2D6*1/*1 and CYP2D6*1/*10 genotype were classified as extensive metabolizers (EM) and the 6 participants with the CYP2D6*10/*10 genotype were classified as intermediate metabolizers (IM) [6, 23].

### Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>*1/*1 (n = 6)</th>
<th>*1/*10 (n = 6)</th>
<th>*10/*10 (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(C_{max}) (ng/mL)</td>
<td>0.453 (0.293–0.702)</td>
<td>1.50 (1.14–1.98)</td>
<td>5.11 (3.13–8.34)</td>
</tr>
<tr>
<td>(T_{max}) (h)</td>
<td>(2.50, 0.75–3.00)</td>
<td>(2.00, 1.00–4.00)</td>
<td>(2.50, 2.00–3.00)</td>
</tr>
<tr>
<td>AUC_{0–24} (ng·h/mL)</td>
<td>2.86 (1.79–4.58)</td>
<td>10.1 (7.44–13.6)</td>
<td>37.2 (25.9–53.4)</td>
</tr>
<tr>
<td>AUC_{0–∞} (ng/mL·h)</td>
<td>2.97 (1.80–4.98)</td>
<td>10.8 (7.75–15.1)</td>
<td>44.4 (30.6–64.4)</td>
</tr>
<tr>
<td>(T_{1/2}) (h)</td>
<td>6.47 ± 2.68</td>
<td>7.00 ± 0.71</td>
<td>8.84 ± 1.70</td>
</tr>
<tr>
<td>CL/F (L/h)</td>
<td>5384 (3324–8990)</td>
<td>1423 (1018–1990)</td>
<td>338 (233–490)</td>
</tr>
<tr>
<td>MR</td>
<td>0.0102 (0.00432–0.0239)</td>
<td>0.0214 (0.0101–0.0453)</td>
<td>0.101 (0.0579–0.175)</td>
</tr>
<tr>
<td><strong>After ZJP</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(C_{max}) (ng/mL)</td>
<td>1.18 (0.732–1.91)</td>
<td>2.55 (1.61–4.05)</td>
<td>4.51 (2.83–7.20)</td>
</tr>
<tr>
<td>(T_{max}) (h)</td>
<td>(2.00, 1.00–4.00)</td>
<td>(2.00, 2.00–3.00)</td>
<td>(3.00, 1.50–4.00)</td>
</tr>
<tr>
<td>AUC_{0–24} (ng·h/mL)</td>
<td>8.58 (5.71–12.9)</td>
<td>17.2 (11.7–25.2)</td>
<td>40.8 (26.7–62.4)</td>
</tr>
<tr>
<td>AUC_{0–∞} (ng/mL·h)</td>
<td>10.0 (6.16–16.3)</td>
<td>19.2 (13.0–28.2)</td>
<td>51.3 (32.5–80.8)</td>
</tr>
<tr>
<td>(T_{1/2}) (h)</td>
<td>8.09 ± 2.72</td>
<td>8.19 ± 0.95</td>
<td>10.4 ± 1.66</td>
</tr>
<tr>
<td>CL/F (L/h)</td>
<td>1580 (971–2571)</td>
<td>812 (550–1199)</td>
<td>293 (186–461)</td>
</tr>
<tr>
<td>MR</td>
<td>0.0512 (0.0178–0.148)</td>
<td>0.0886 (0.0530–0.148)</td>
<td>0.132 (0.0892–0.196)</td>
</tr>
</tbody>
</table>

Data are presented as geometric mean(90% CI), except for \(T_{1/2}\), which is presented as arithmetic mean ± standard deviation, and \(T_{max}\), which is presented as median (range). Compared with *1/*1: \# \(p<0.05\); Compared with baseline: \* \(p<0.05\).

**Fig. 2** Individual oral clearance (CL/F) of dextromethorphan in healthy Chinese volunteers with the CYP2D6*1/*1 genotype (n = 6), CYP2D6*1/*10 genotype (n = 6), and CYP2D6*10/*10 genotype (n = 6) who received a 15-mg dextromethorphan hydrobromide tablet before (open circles) and after (closed circles) 7 days of treatment with ZJP (3 g twice daily).

**Fig. 3** Individual urinary metabolic ratios (MR) of dextromethorphan to dextrorphan in healthy Chinese volunteers with the CYP2D6*1/*1 genotype (n = 6), CYP2D6*1/*10 genotype (n = 6), and CYP2D6*10/*10 genotype (n = 6) who received a 15-mg dextromethorphan hydrobromide tablet before (open circles) and after (closed circles) 7 days of treatment with ZJP (3 g twice daily).
The observed inhibition of CYP2D6-mediated metabolism of dextromethorphan indicates the potential for ZJP to interact with other drugs metabolized by this enzyme. This study demonstrated that ZJP can have a moderate effect on the pharmacokinetics of a drug that is metabolized by CYP2D6 in people who are CYP2D6 EMs. So, the interactions between ZJP and other CYP2D6 substrates in Chinese people with CYP2D6*10 alleles should also be investigated.

Co-administration of ZJP and CYP2D6 substrates for which only a metabolite is active should be avoided because the inhibitory effects of ZJP on CYP2D6 can prevent the active metabolite from forming and producing the desired therapeutic effect. ZJP could be used as a bioenhancer in clinical practice, since it significantly increases the plasma concentration of CYP2D6 substrates for which the parent drug is active [25, 26], particularly in people with the CYP2D6*1/*1 and CYP2D6*1/*10 genotypes. Of course, caution is warranted when ZJP is co-administered with CYP2D6 substrates that have relatively narrow therapeutic windows.

Although we did not test for any clinical effects, changes of this magnitude in other 2D6 substrates are likely large enough to result in changes in clinical drug response, affecting either efficacy or toxicity. Some drugs metabolized by CYP2D6 (e.g., tricyclic antidepressants, selective serotonin reuptake inhibitors, opioids, anti-arrhythmics, antipsychotics, and some beta-blockers) have a relatively narrow therapeutic window. Overall, these results suggested that there is a potential for interactions between ZJP and conventional drugs metabolized mainly CYP2D6 when administered concomitantly. Caution warranted when ZJP is co-administered with CYP2D6 substrates, especially those with narrow therapeutic index.

The daily dose of ZJP administered in our study was 6 g orally. Plasma concentrations of coptisine and berberine were not determined, but the significant inhibition of CYP2D6 in the CYP2D6*1/*1 and CYP2D6*1/*10 groups indicates that coptisine and berberine can cross the intestinal mucosa when ZJP is taken orally and an inhibitory concentration of coptisine and berberine in ZJP toward CYP2D6 can be reach in the liver because of tissue distribution [27, 28].

In conclusion, these data demonstrated that administration of Zuojin Pill inhibited moderately CYP2D6-mediated metabolism of dextromethorphan in healthy volunteers. The inhibitory influence of CYP2D6 was greater in CYP2D6*1/*1 and CYP2D6*1/*10 groups than CYP2D6 *10/*10 groups. The inhibition of CYP2D6 by ZJP could result in clinically relevant effects, either beneficial or deleterious, depending on the nature of the CYP2D6 genotype.

Acknowledgments This work was supported by the National Natural Science Foundation of the People’s Republic of China (Grant 81173118), the National Key New Drug Creation Special Programme (Grant...
2012ZX09303009-001), and the Shanghai Key Lab of Traditional Clinical Medicine (Grant C10dz2220200).

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflicts of interest.

References
