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Relative bioavailability and pharmacokinetic comparison of two different enteric formulations of omeprazole*

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Abstract: In order to comply with the requirements for a drug listed in China, the study was developed to compare the pharmacokinetics and relative bioavailability of two different enteric formulations of omeprazole (OPZ) in healthy Chinese subjects. A total of 32 volunteers participated in the study. Plasma concentrations were analyzed by non-stereospecific liquid chromatography/tandem mass spectrometric (LC-MS/MS) method. After administration of a single 40-mg dose of the two OPZ formulations, the comparative bioavailability was assessed by calculating individual AUC_{0-t} (the area under the concentration-time curve from time zero to the last measurable concentration), $AUC_{0-\infty}$ (the area under the concentration-time curve extrapolated to infinity), C_{max} (the maximum observed concentration), and T_{peak} (the time to C_{max}) values of OPZ, 5-hydroxyomeprazole (OH-OPZ), and omeprazole sulfone (OPZ-SFN), respectively. The 90% confidence intervals (CIs) of AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} were 85.4%–99.0%/88.8%–98.6%/87.6%–99.4%, 85.5%–99.2%/89.0%–98.6%/88.5%–101.3%, and 72.3%–87.6%/79.6%–91.1%/88.4%–99.1% for OPZ/OH-OPZ/OPZ-SFN, respectively, and T_{peak} values did not differ significantly. In this study, the test formulation of OPZ in fasting healthy Chinese male volunteers met the Chinese bioequivalance standard to the reference formulation based on AUC, C_{max}, and T_{peak}.

Key words: Omeprazole, 5-Hydroxyomeprazole, Omeprazole sulfone, Bioavailability, Pharmacokinetics, Liquid chromatography/tandem mass spectrometry (LC-MS/MS)

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1 Introduction

Omeprazole (OPZ), a substituted benzimidazole (5-methoxy-2-{[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl]sylfonyl}-1H-benzimidazole), is a proton pump inhibitor (PPI), which decreases acid production in the stomach and is used for treating various acid-related diseases, such as peptic ulcer, gastroesophageal reflux diseases, and Zollinger-Ellison syndrome (Blum, 1996; Kanazawa *et al.*, 2003; Rezk *et al.*, 2006; Sachs *et al.*, 2006; Poo *et al.*, 2008).

The pharmacokinetics and pharmacodynamics of OPZ significantly depend on CYP2C19 genotype status (Hu *et al.*, 2007). CYP2C19 polymorphism frequency has marked interethnic differences. The poor metabolizer phenotype is present in 15%–17% of Chinese population but only in approximately 2%–6% of Caucasians (Bertilsson *et al.*, 1992). In the liver, the formation of 5-hydroxyomeprazole (OH-OPZ) is mainly mediated by CYP2C19, but the formation of omeprazole sulfone (OPZ-SFN) is

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metabolized by CYP3A4 then to hydroxyomeprazole sulfone. OPZ has a 10-fold lower affinity for CYP3A4 (Andersson *et al.*, 1992; 1994). OPZ is most affected by CYP2C19 polymorphism of the main PPIs. Thus, it seems insufficient that the evaluation of fasting comparative bioavailability of the two formulations in the Chinese population is only based on determination of the parent drug. There are several articles reported of OPZ alone or in combination with its main metabolites OH-OPZ and OPZ-SFN in human serum or plasma.

In China, the bioequivalence studies are mandatory for generic drugs registered. Bioequivalence of two formulations of the same drug has been concluded based on the lack of differences in primary pharmacokinetic parameters of bioavailability study such as the rate (maximal concentration C_{max}) and extent (area under the blood concentration-time curve AUC) of absorption (SFDA, 2005).

Various studies have investigated the pharmacokinetic properties and bioequivalence of OPZ (Allegrini *et al*., 2008; Joti *et al*., 2009; Rhim *et al*., 2009); however, no data was found to make the main metabolites of OPZ as a clinical concern in the evaluation of bioequivalence of OPZ formulations. This study was then designed to compare the pharmacokinetic properties and relative bioavailability of two different enteric formulations of OPZ 20 mg after single oral administration (40-mg dose) in fasting, healthy Chinese male volunteers by determination of OPZ, OH-OPZ, and OPZ-SFN in human plasma.

2 Subjects and methods

2.1 Study design

This study was performed according to the revised Declaration of Helsinki for biomedical research involving human subjects (http://www.wma.net/en/30publications/10policies/b3/index.html) and the Guideline for Good Clinical Practice recommended by the State Food and Drug Administration (SFDA, 2003) of China. The protocol of this study was approved by the ethics committee of the First Affiliated Hospital, School of Medicine, Zhejiang University (Hangzhou, Zhejiang, China). Before all participants signed a written informed consent, they had been informed of the contents and possible risk of the study prior to any screening procedures. Subjects were compensated for their time and transportation costs, whether they completed the study or not. There were no benefits from commercial sources for the work reported in this article. The authors have indicated that they have no conflicts of interest regarding the content of this article.

A clinical screening procedure including a physical examination and laboratory tests which included hematology, blood biochemistry, urine analysis, and hepatitis B and human immunodeficiency virus (HIV) antibodies, was undertaken before eligible subjects were selected. At the same time, the authorized investigators recorded medical history, body weight, height, vital signs, and a 12-lead electrocardiogram. Volunteers who had a history or evidence of a hepatic, renal, gastrointestinal, or hematologic abnormality or any acute or chronic diseases, or an allergy to any drugs were excluded. This was undertaken to ensure the safety of subjects and no influence on the drug safety evaluation. All volunteers avoided using other drugs during the entire trial process (from prior to the study to its completion). The whole process lasted at least four weeks. All subjects did not participate in other clinical trials within three months. Screening procedures were repeated at the end of the trial.

A monocentric, open-label, single-dose, randomized-sequence, two-way crossover study design was adopted, in which 32 healthy male volunteers were assigned to one of two treatment sequences (test-reference or reference-test) according to a computer-generated randomization schedule [The trial was divided into two parts: pre-trial, with 4 volunteers according to a computer-generated randomization schedule (SAS 9.0, seed=2009, block=2, random_code=2); and formal trial, with 28 volunteers according to a computer-generated randomization schedule (SAS 9.0, seed=20090522, block=14, random_code=2)]. Volunteers were hospitalized in the study wards at about 8:00 p.m. one day before this study and fasted for at least 10 h before each drug administration. On the morning of the administration day, the subjects received a single 40-mg dose (administered with 250 ml of water) of the test (consisting of OPZ enteric capsule 20 mg, manufactured by Jiangsu Hengrui Medicine Co., Ltd., China; Lot: 20090212, expiration: 2011-02-11) or the reference

(consisting of OPZ enteric tablet 20 mg, trade mark LOSEC MUPS®, manufactured by AstraZeneca AB, Södertälje, Sweden; Lot: KG8823, expiration: 2011.6). Drinking water and food intake were allowed 2 and 4 h after administration, respectively. There was a one-week washout between the two treatment periods.

2.2 Blood sampling

During both treatment periods, free flowing blood samples (~5 ml) were collected from a suitable forearm vein using an indwelling catheter [20 G× 1.16 in (1.1 mm×30.0 mm), BD-InSyte, Becton Dickinson, Suzhou, China] into heparin anticoagulated tubes [containing 0.5 ml of 0.4% heparin sodium (4 g/L)] before (0 h) and 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 15.0, 24.0 h after dosing. After each blood sample was drawn, 1 ml of sodium heparin (25 U/ml) was injected into the catheter to ensure that there was no blood clot in it. The next time point, before collection of blood samples, 1 ml of blood was drawn from the angiocatheter and discarded. The blood samples were centrifuged at 3452×*g* and 4 °C with a refrigerated centrifuger (Eppendorf 5417c, Eppendorf, Germany) for 15 min, and plasma samples were kept at −70 °C until used.

2.3 Determination of OPZ, OH-OPZ, and OPZ-SFN in human plasma

Plasma concentrations of the parent OPZ and its metabolites OH-OPZ and OPZ-SFN were determined by a nonstereospecific liquid chromatography/tandem mass spectrometric (LC-MS/MS) method. Plasma (200 μl) plus 20 μl of methanol and 20 μl of lansoprazole (internal standard, 53.4 ng/ml) was extracted with 1 ml of chloroform. The samples were then vortex-mixed for 2 min and centrifuged for 5 min at 13000 r/min (Adventurer AR1140, OHAUS, USA). The upper aqueous phase was discarded and the lower chloroform layer was transferred into another tube and evaporated to dryness under a nitrogen stream at 25 °C, protected from light. Samples were reconstituted in 100 μl of methanol (adjusted to pH 9.3 with ammonia) and 2 μl supernatant was injected for LC-MS/MS.

The high-performance liquid chromatography (HPLC) was performed on an Agilent 1100 system equipped with a Gl311A quaternary-dimension infusion pump, a G1367A autosampler, a Gl379A vacuum degasser, and a G1316A column thermostat (Agilent 1100, Agilent Technologies Inc., Santa Clara, California, USA). The LC system was coupled to an Agilent Technologies 6410 mass spectrometer (Agilent Technologies Inc., Santa Clara, California, USA) via a TurboIonspray ionization (ESI) interface for mass analysis and detection. Data acquisition and analysis were accomplished with Agilent MassHunter Workstation B.01.00.

The chromatographic column was an Agilent Zorbax SB-C_{18} (3.0 mm×150.0 mm, 3.5 μm) at a column temperature of 20 °C. An isocratic mobile phase consisting of methanol-water (73:27, v/v) was used at a flow rate 0.34 ml/min, with the injection volume of 2 μl. Prior to the analytical column, a C_{18} guard column (Agilent Technologies Inc.) was placed to prevent column degradation.

All measurements were operated under the negative ESI mode. The spray voltage was set at 4000 V. Nitrogen was used as nebulizer gas and nebulizer pressure was set at 45 psi (1 psi=6.895 kPa). Desolvation gas (nitrogen) temperature was set at 350 °C with a flow-rate of 8 L/min. High purity nitrogen was used as collision gas with a pressure of 0.1 MPa for collision-induced dissociation (CID). Using multiple reaction monitoring (MRM)-mode for quantification at mass-to-charge ratio (*m*/*z*) 344.1→194.0 (fragmentation energy=100 V, collision energy=10 V) for OPZ, *m*/*z* 360.1→194.0 (fragmentation energy=100 V, collision energy=10 V) for OH-OPZ, *m*/*z* 360.1→146.0 (fragmentation energy=145 V, collision energy=25 V) for OPZ-SFN, and *m*/*z* 368.2→164.1 (fragmentation energy=120 V, collision energy=20 V) for lansoprazole.

The four pairs of ions were monitored simultaneously within the analytic procedure. Under these conditions, the method was linear over the concentration range from 5.04 to 2016.00 ng/ml for OPZ, 5.00 to 2000.00 ng/ml for OH-OPZ, and 3.63 to 1452.00 ng/ml for OPZ-SFN. The calibration curves were obtained and assayed along with quality control (QC) samples and each batch of clinical plasma samples. QC samples were prepared in drug-free plasma (purchased from the Blood Center of Zhejiang Province, China) at concentrations of 8.06, 80.64, 806.40, and 1209.60 ng/ml for OPZ, 8.00, 80.00, 800.00, and 1200.00 ng/ml for OH-OPZ, and 5.81, 58.08, 580.80, and 871.20 ng/ml for OPZ-SFN, in the

same manner as standard curves. Then, the calibration standards and QC samples were prepared following the sample preparation procedure. Independently, the QC samples were prepared and analyzed with test samples at intervals in each run. The results of the QC were qualified to determine accepting or rejecting the run.

According to the requirements of SFDA (SFDA, 2005) guidance on bioanalytic method validation, the mean values of QC should be within 15% of the actual value. QC at the lower limit of quantitation (LLOQ) was not restricted by ≤15% but should be less than 20%. The LLOQ was established at 5.04, 5.00, and 3.63 ng/ml for OPZ, OH-OPZ, and OPZ-SFN, respectively with deviation ≤±20% and coefficient of variation (CV) ≤7.3% for all analytes. Overall, the intra- or interassay precision of OPZ, OH-OPZ, or OPZ-SFN was no more than 9.93% of each QC levels, and intra- or interassay accuracy (the accuracy was expressed as the percent ratio between the experimental concentration and the nominal concentration for each sample) was within (100±15)%. Prior to study initiation, the stability was studied under a variety of storage and handling conditions. It was discovered that the three analytes were stable for at least three freeze-thaw cycles and for at least 6 h at room temperature. The QC plasma samples also showed no loss of analytes when they were stored for 20 d at −20 °C, and the processed plasma samples showed no significant degradation in the LC autosampler for at least 12 h.

2.4 Tolerability

At baseline and after completion of the study, physical examination was done and vital signs including blood pressure, heart rate, respiratory rate, and body temperature were monitored. Routine blood and urine tests, blood biochemical tests (hepatic and renal function), and 12-lead electrocardiograph (ECG) were also performed. Subjects were under continuous medical supervision by two physicians during the hospitalization. Tolerability was assessed by the authorized investigators based on vital signs, physical examination, subject interviews, spontaneous reporting, and clinical laboratory tests during the whole study period. All adverse events (AEs) were recorded in the source data record and on case-report forms.

All clinical laboratory tests were performed at the First Affiliated Hospital, School of Medicine, Zhejiang University, China. The internal quality controls of laboratory tests were performed at least twice a day. The clinical laboratory regularly participated in the external quality assessment of the National Center for Clinical Laboratory and the College of American Pathologists (CAP).

2.5 Pharmacokinetic and statistical analyses

After oral administration, the following parameters were determined by a noncompartmental analysis using DAS 2.0 (Wannan Medical College, Wuhu, China): C_{max} (the maximum observed concentration), T_{peak} (the time to the C_{max}), AUC_{0-t} (the area under the concentration-time curve from time zero to the last measurable concentration, which is calculated by the trapezoidal rule), $AUC_{0-\infty}$ (the area under the concentration-time curve extrapolated to infinity, according to the relationship $AUC_{0-\infty}=AUC_{0-t}+c_t/k_e$, where c_t is the last concentration evaluated in plasma greater than LLOQ and the elimination rate (k_e) is obtained as the slope of the linear regression of the log-transformed concentration-time curve data in the terminal phase), and $t_{1/2}$ (the elimination half-time, which is estimated using the equation $t_{1/2}=\ln 2/k_e$). The relative bioavailability (F) of the test formulation was calculated as follows: $F=AUC_{0-t(test)}/AUC_{0-t(reference)}\times 100\%$.

The bioequivalence study recommended by the Chinese regulatory guideline (SFDA, 2005) was assessed by calculating individual AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, and T_{pesk} values. Analysis of variance (ANOVA) using Das 2.0 was performed on AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} evaluating for treatment, period, sequence, and subject within sequence effects. The significance level was set at α=0.05. Their ratios (test versus reference) of log-transformed data were analyzed for relative bioavailability. Ninety percent confidence intervals (90% CIs) served as interval estimates and were determined by two one-sided t-tests (Bolton, 1997). If the parameters between the two formulations were not statistically different from each other, and the log-transformed ratios of C_{max} and AUC located within the predetermined equivalence range (SFDA, 2005) (70%–143% for C_{max} and 80%–125% for AUC) as established by the SFDA, the two formulations would be considered bioequivalent. With

regard to T_{peak}, a nonparametric test with $P>0.05$ suggests that the test and reference formulations had no significant differences.

3 Results

3.1 Volunteer characteristics

A total of 32 healthy Chinese male subjects [age (23.28±1.92) years, range 19–27 years; weight, (62.72±6.82) kg, range 51–78 kg; height, (172.03±4.92) cm, range 160–184 cm] were enrolled in the study. Sixteen subjects received the test formulation first. All volunteers completed the study.

3.2 Pharmacokinetics and bioavailability evaluation

Profiles of the mean plasma concentration versus time curves are shown in the Fig. 1. The pharmacokinetic parameters (AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{peak}, $t_{1/2}$, and relative bioavailability F) are summarized in Table 1. It was found no formulation, sequence, or period effects for any pharmacokinetic parameters by ANOVA. Significant differences were not found between the formulations in C_{max}, AUC_{0-t}, or $AUC_{0-\infty}$.

The 90% CIs of the ratios (test/reference) for the log-transformed values of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ of OPZ, OH-OPZ, and OPZ-SFN are listed in Table 2. For the parent OPZ, the 90% CIs were 72.3% to 87.6%, 85.4% to 99.0%, and 85.5% to 99.2%, respectively, for the log-transformed values of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$. For the metabolite OH-OPZ, the 90% CIs were 79.6% to 91.1%, 88.8% to 98.6%, and 89.0% to 98.6%, respectively. For the metabolite OPZ-SFN, the 90% CIs were 88.4% to 99.1%, 87.6% to 99.4%, and 88.5% to 101.3%, respectively.

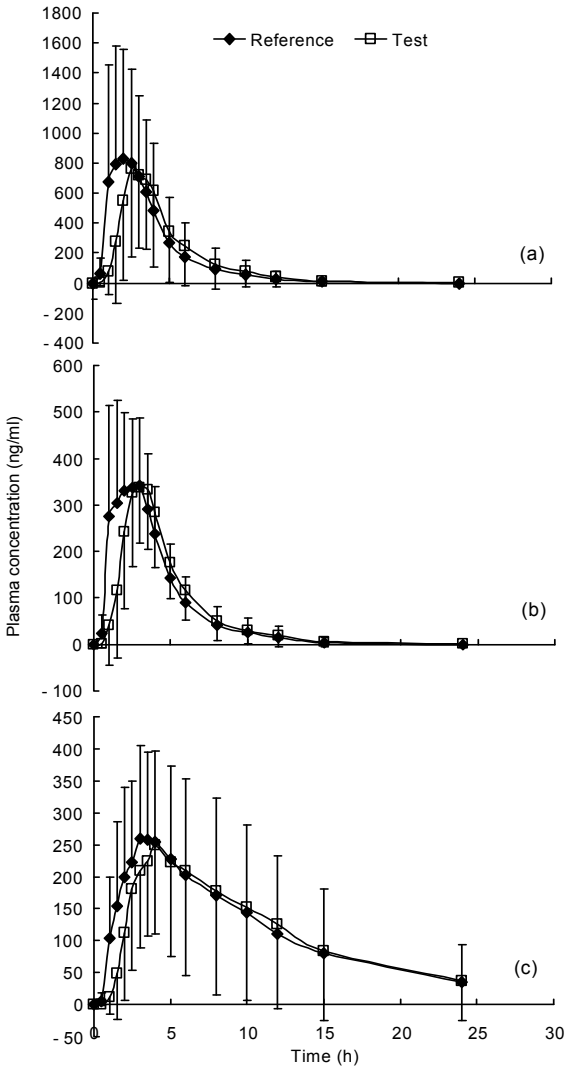

Fig. 1 Plasma concentration-time profiles of parent omeprazole (OPZ) (a), its metabolites 5-hydroxyomeprazole (OH-OPZ) (b) and omeprazole sulfone (OPZ-SFN) (c) after administration of a single 40-mg dose of test and reference formulations of OPZ in healthy Chinese male volunteers

Data are expressed as mean±SD (n=32)

Table 1 Pharmacokinetic parameters of OPZ and its metabolites OH-OPZ and OPZ-SFN after a single 40-mg oral dose of test and reference formulations of OPZ in healthy Chinese male volunteers

Compound	Formulation	C_{max} (ng/ml)	T_{peak} (h)	AUC_{0-t} (ng·h/ml)	$AUC_{0-\infty}$ (ng·h/ml)	$t_{1/2}$ (h)	F (%)
OPZ	Test	1023.67 (542.30)	2.63 (0.67)	3152.80 (2760.03)	3185.01 (2795.76)	1.23 (0.70)	94.54 (22.19)
	Reference	1330.46 (758.07)	2.02 (0.84)	3467.04 (3028.47)	3495.09 (3058.41)	1.07 (0.64)	
OH-OPZ	Test	451.20 (106.54)	2.77 (0.76)	1448.39 (438.90)	1474.94 (452.78)	1.45 (0.78)	94.87 (15.76)
	Reference	531.00 (129.91)	2.08 (0.91)	1545.59 (446.06)	1571.41 (458.53)	1.33 (0.60)	
OPZ-SFN	Test	279.62 (147.34)	3.81 (1.47)	2673.48 (2505.51)	3093.78 (3265.50)	4.14 (2.58)	95.26 (18.93)
	Reference	292.79 (139.12)	2.97 (1.18)	2794.04 (2472.57)	3147.52 (3082.48)	3.93 (2.28)	

Data are mean (SD) (n=32). Formulations: test (manufactured by Jiangsu Hengrui Medicine Co., Ltd., China) and reference (trade mark LOSEC MUPS®, manufactured by AstraZeneca AB, Södertälje, Sweden). OPZ: omeprazole; OH-OPZ: 5-hydroxyomeprazole; OPZ-SFN: omeprazole sulfone; C_{max}: maximum observed concentration; T_{peak}: time to the C_{max}; AUC_{0-t}: area under the concentration-time curve from time zero to the last measurable concentration; $AUC_{0-\infty}$: area under the concentration-time curve extrapolated to infinity; $t_{1/2}$: elimination half-time; F: relative bioavailability

Table 2 Comparison of 90% CIs of logarithm-transformed parameters of OPZ and its metabolites OH-OPZ and OPZ-SFN after a single 40-mg oral dose of test and reference formulations of OPZ in healthy Chinese male volunteers

Compound	$\ln C_{max}$		$\ln AUC_{0-t}$		$\ln AUC_{0-\infty}$	
	T/R ratio (%)	90% CI (%)	T/R ratio (%)	90% CI (%)	T/R ratio (%)	90% CI (%)
OPZ	79.6	72.3–87.6	91.9	85.4–99.0	92.1	85.5–99.2
OH-OPZ	85.1	79.6–91.1	93.6	88.8–98.6	93.7	89.0–98.6
OPZ-SFN	93.6	88.4–99.1	93.3	87.6–99.4	94.7	88.5–101.3

n=32. Formulations: test (manufactured by Jiangsu Hengrui Medicine Co., Ltd., China) and reference (trade mark LOSEC MUPS®, manufactured by AstraZeneca AB, Södertälje, Sweden). OPZ: omeprazole; OH-OPZ: 5-hydroxyomeprazole; OPZ-SFN: omeprazole sulfone; C_{max}: maximum observed concentration; AUC_{0-t}: area under the concentration-time curve from time zero to the last measurable concentration; $AUC_{0-\infty}$: area under the concentration-time curve extrapolated to infinity; T/R: test/reference; CI: confidence interval

The corresponding ratios of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ of OPZ, OH-OPZ, and OPZ-SFN met the predetermined criteria for bioequivalence (all $P<0.05$), which indicates that the C_{max} and AUC of OPZ, OH-OPZ, and OPZ-SFN did not differ significantly after the test or reference drug administration. The relative bioavailability F of the test formulation to the reference formulation was 94.54% for OPZ, 94.87% for OH-OPZ, and 95.26% for OPZ-SFN. The OPZ T_{peak} values after the administration of the two formulations did not differ significantly ($P>0.05$, P values were 0.663, 0.563, and 0.172 for OPZ, OH-OPZ, and OPZ-SFN, respectively).

3.3 Tolerability

Both the test and reference formulations of OPZ appeared well tolerated in the population studied when administered orally. Two adverse events were reported during the trial, including one case of mild nausea with the reference preparation and one case of mild nausea with the test preparation. The symptoms disappeared after eating at noon. No volunteers were withdrawn as a result of adverse events. No serious adverse events were found.

4 Discussion

This study applied a validated nonstereospecific LC-MS/MS method to simultaneously determine OPZ and its metabolites, OH-OPZ and OPZ-SFN, in human plasma. This study compared the pharmacokinetic properties and relative bioavailabilities of two different enteric formulations of OPZ in fasting healthy Chinese male volunteers by this method. According to subjects' self-reports and from the vital signs and laboratory tests, there were no AEs found during the whole study.

For AUC reflects the extent of drug absorption and C_{max} and T_{peak} are important features of the plasma level profile, these parameters are characteristics of the drug formulation and all important for comparative bioavailability (bioequivalence) studies. The 90% CIs of the test/reference ratios of AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} for OPZ, OH-OPZ, and OPZ-SFN were contained within predefined bioequivalence criteria (80%–125% for AUC and 70%–143% for C_{max}) (SFDA, 2005) established by the SFDA of China. It suggests that formulation, sequence, or period had no statistically significant effect on AUC_{0-t}, $AUC_{0-\infty}$, or C_{max} of OPZ, OH-OPZ, or OPZ-SFN at the significance level of 0.05.

Some methods have been reported to simultaneously determine OPZ, OH-OPZ, and OPZ-SFN in human plasma (Rezk *et al.*, 2006; Rambla-Alegre *et al.*, 2009). However, the nonstereospecific LC-MS/MS method adopted in this article has not been reported previously. At the same time, there are few reports regarding OPZ metabolites as a clinical concern for evaluation of comparative bioavailability of OPZ formulations. In our research, these two metabolites were involved in comparative bioavailability studies as one of the important indicators.

Comparison with published data shows that parameters of OPZ determined in the current study are not closely in accordance with data reported in the literature from healthy volunteers. Poo *et al.* (2008) have reported that OPZ capsules 20 mg orally administered to 34 healthy Mexican volunteers produced mean reference (test) AUC_{0-t}, C_{max}, T_{peak}, and $t_{1/2}$ of 0.88 (0.92) μg·h/ml, 0.49 (0.48) μg/ml, 1.9 (2.0) h, and 0.85 (0.91) h, respectively. Allegrini *et al.* (2008) have found that OPZ capsules (20 mg) in 50 healthy Italian male and female volunteers produced a mean reference (test) AUC_{0-t}, C_{max}, T_{peak}, and $t_{1/2}$ of 908.95 (900.83) ng·h/ml, 447.61 (436.31) ng/ml,

2 (2) h, and 1.27 (1.06) h, respectively. Rhim *et al.* (2009)'s study in healthy Korean male volunteers administered with OPZ 20 mg reported AUC_{0-t} of 1223.3 ng·h/ml, C_{max} of 598.7 ng/ml, T_{peak} of 1.9 h, and $t_{1/2}$ of 1.3 h for reference, and AUC_{0-t} of 1284.3 ng·h/ml, C_{max} of 598.1 ng/ml, T_{peak} of 1.9 h, and $t_{1/2}$ of 1.4 h for test. However, in the present study, the AUC_{0-t}, C_{max}, T_{peak}, and $t_{1/2}$ were 3467.0 and 3152.8 ng·h/ml, 1330.5 and 1023.7 ng/ml, 2.02 and 2.63 h, 1.07 and 1.23 h, respectively, for reference and test, following administration of OPZ 40 mg enteric formulations. These differences may be due to the different race, especially for CYP2C19 genotypes that influence the body's handling of OPZ.

The single-dose design and only healthy young male volunteers in fasting conditions included are major limitations of the study. The data of healthy volunteers do not represent the patients. Although no statistically significant differences in pharmacokinetic parameters between the two formulations were found, it cannot predict the disposition of the drug in patients. The mean age of these healthy subjects was 23.28 years (range, 19–27 years) and, therefore, the study results cannot be extrapolated to an older population and children. There is also a need for a larger study in women.

5 Conclusions

In this study, a single 40-mg dose of the test formulation of OPZ in fasting healthy Chinese male volunteers met Chinese regulatory criteria for assumption of bioequivalence to the reference formulation based on AUC, C_{max}, and T_{peak}. Both formulations were well tolerated.

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