PO Box 2345, Beijing 100023, China
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BASIC RESEARCH

Pharmacokinetics and bioequivalence of ranitidine and bismuth derived from two compound preparations

Quan Zhou, Zou-Rong Ruan, Hong Yuan, Bo Jiang, Dong-Hang Xu

Quan Zhou , Zou-Rong Ruan, Hong Yuan, Bo Jiang, Dong-Hang Xu, Department of Clinical Pharmacology, the 2nd Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou 310009, Zhejiang Province, China
Co-correspondence: Zou-Rong Ruan
Correspondence to: Associate Professor, Quan Zhou, Division of Clinical Pharmacology, the 2nd Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou 310009, Zhejiang Province, China. zhouquan142602@zju.edu.cn
Telephone: +86-571-87783891 Fax: +86-571-87213864
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Abstract

AIM: To evaluate the bioequivalence of ranitidine and bismuth derived from two compound preparations.

METHODS: The bioavailability was measured in 20 healthy male Chinese volunteers following a single oral dose (equivalent to 200 mg of ranitidine and 220 mg of bismuth) of the test or reference products in the fasting state. Then blood samples were collected for 24 h. Plasma concentrations of ranitidine and bismuth were analyzed by high-performance liquid chromatography and inductively coupled plasma-mass spectrometry (ICP-MS), respectively. The non-compartmental method was used for pharmacokinetic analysis. Log-transformed C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ were tested for bioequivalence using ANOVA and Schuirmann two-one sided *t*-test. T_{max} was analyzed by Wilcoxon's test.

RESULTS: Various pharmacokinetic parameters of ranitidine derived from the two compound preparations, including C_{max}, $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, T_{max} and $T_{1/2}$, were nearly consistent with previous observations. These parameters derived from test and reference drug were as follows: C_{max} (0.67 ± 0.21 *vs* 0.68 ± 0.22 mg/L), $AUC_{(0-t)}$ (3.1 ± 0.6 *vs* 3.0 ± 0.7 mg/L per hour), $AUC_{(0-\infty)}$ (3.3 ± 0.6 *vs* 3.2 ± 0.8 mg/L per hour), T_{max} (2.3 ± 0.9 *vs* 2.1 ± 0.9 h) and $T_{1/2}$ (2.8 ± 0.3 *vs* 3.1 ± 0.4 h). In addition, double-peak absorption profiles of ranitidine were found in some Chinese volunteers. For bismuth, those parameters derived from test and reference drug were as follows: C_{max} (11.80 ± 7.36 *vs* 11.40 ± 6.55 μg/L), $AUC_{(0-t)}$ (46.65 ± 16.97 *vs* 47.03 ± 21.49 μg/L per hour), T_{max} (0.50 ± 0.20 *vs* 0.50 ± 0.20 h) and $T_{1/2}$ (10.2 ± 2.3 *vs* 13.0 ± 6.9 h). Ninety percent of confidence intervals for the test/reference ratio of C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ derived from both ranitidine and bismuth were found within the bioequivalence acceptable range of 80%-125%. No significant difference was found in T_{max} derived from both ranitidine and bismuth.

CONCLUSION: The two compound preparations are bioequivalent and may be prescribed interchangeably.

Key words: Ranitidine; Bismuth; Compound preparation; Bioequivalence; Pharmacokinetics; Healthy volunteers; High-performanace liquid chromatography; Inductively coupled plasma-mass spectrometry

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INTRODUCTION

Ranitidine is a very common histamine H_2 receptor antagonist. It exerts most prominent effect on basal acid secretion and less profound effect on acid production[1,2]. Bismuth potassium citrate has mucosal protective effects by blocking pepsin activity, retarding hydrogen-ion back-diffusion and stimulating prostaglandin synthesis. In addition, it has an inhibitory effect on *Helicobacter pylori* (*H pylori*)[3-6]. Thus, ranitidine and bismuth potassium citrate have a synergistic effect and are usually concurrently prescribed in poly-therapy regimens for gastroduodenal ulcers and *H pylori* infection. Especially, the availability of ranitidine bismuth citrate and compound preparation of ranitidine and bismuth potassium citrate in market makes administration more conveniently and increases medication compliance in ulcer patients[7,8].

The pharmacokinetics of ranitidine has been described previously[9-11]. After oral administration 50% of ranitidine is absorbed, resulting in the peak serum concentration of 2 ± 3 h after dosing, followed by elimination with a half-life of 2.5 ± 3 h. Ranitidine is metabolized to a small extent, primarily via flavin mono-oxygenases[12]. It is eliminated through kidney, with approximately 70% of the systemically available dose recovered in urine as unchanged drug. Bismuth is only minimally absorbed and its bioavailability ranges 0.16%-0.28%, but the median peak bismuth concentration occurs 30 min (range 15-105

min) post-dosing[13,14]. The concentration of bismuth in kidneys is high and it is also retained there for a long time. Elimination from blood displays multi-compartment pharmacokinetics[15].

Comparative bioavailability of different mono-preparations of ranitidine hydrochloride or colloidal bismuth sub-citrate in healthy volunteers or patients has been described previously[16-20]. However, to our knowledge, there is no report on the pharmacokinetic and bioequivalence evaluation of compound preparations containing these two drugs.

MATERIALS AND METHODS

Drugs and reagents

Ranitidine reference substance (purity> 99.5%) was provided by Shuguang Pharmaceutical Factory (Beijing, China). Bi_2O_3 reference substance (purity> 99.999%) and TlCl reference substance (purity> 99%) were provided by ALDRICH Chemical Company (USA). Nitric acid was of MOS grade. Ultra pure water was obtained from Milli-Q Academic (Millipore Co., USA). Acetonitrile was of HPLC grade. Potassium dihydrogen phosphate and perchloric acid were of analytical grade. Test preparation was compound ranitidine tablet (lot 041201, expiracy: 12/2006) from Chongqing Pharmaceutical Factory (Chongqing, China). Reference preparation was compound ranitidine capsule (lot 041002, expiracy: 9/2006) from Nuode Pharmaceutical Factory (Jiangsu, China). Each tablet or capsule contained ranitidine hydrochloride (equivalent to 100 mg of ranitidine) and bismuth potassium citrate (equivalent to 110 mg of bismuth).

Study subjects

After approval by the Ethics Committee of the 2nd Affiliated Hospital (School of Medicine, Zhejiang University), 20 male healthy Chinese volunteers (age, 24±1 years; weight, 63.8±6.1 kg; BMI, 22.1±1.7 kg/m^2) gave their written informed consent to participate in the study and all of them completed the study. All volunteers were considered to be in good health on the basis of physical examination, electrocardiogram (ECG), and laboratory tests including complete blood count, blood biochemistry testing and urinalysis. Each volunteer was required to be 18-40 years old, a nonsmoker, and to have a BMI between 19 and 25 kg/m^2. Participants were excluded for the following reasons: any significant medical history, history of any localized or systemic infection within 4 wk before admission, use of prescription or over-the counter medication or alcohol within 2 wk before enrollment, history of alcohol or drug abuse, donation of blood within the past 2 mo.

Study design

The study had an open-label, randomized, two-period crossover design, with 1 wk washout between periods. All volunteers were not allowed to take any medications 2 wk before and during the study period. After fasting for l2 h overnight, the volunteers received a single oral dose (equivalent to 200 mg of ranitidine and 220 mg of bismuth) of the test or reference products with 200 mL water in a crossover fashion. No food was allowed until 4 h after dose administration. Water intake was allowed after 2 h of dose. Water, lunch and dinner were given to all volunteers according to a time schedule. The volunteers were under direct medical supervision at the study site. Blood samples (4 mL) were drawn into Vacutainer™ tubes containing K_2EDTA from a forearm vein using an indwelling catheter before drug intake and at 0.17, 0.33, 0.50, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 24 h for the two phases after dosing. Blood samples were centrifuged at 3000 r/min for 10 min, and plasma was separated and stored at -80 ℃ until assay. ECG, biochemical and hematological laboratory tests were performed for each volunteer to record any clinically abnormal finding.

Analytical procedure

High performance liquid chromatography (HPLC) assay method for ranitidine was developed in our laboratory. In brief, 50 μL of perchloric acid solution (2.5 mol/L) was added to 200 μL plasma in the eppendorf tube (1.5 mL). The mixture was vortexed for 20 s and then centrifuged at 36 670 r/min for 10 min. The supernatant was transferred to vial on the rack of autosampler and 50 μL was injected onto the column. The HPLC injection sequence was as follows: calibration standards of 0.02, 0.05, 0.1, 0.2, 0.5, 1.0, 2.0 mg/L, volunteers' plasma samples and quality-control samples of 0.04, 0.4 and 1.5 mg/L throughout all sequences.

The assay method for bismuth was as follows: plasma samples (0.5 mL) were added to Tl (internal standard) working solution and diluted to a volume of 5 mL with super pure water, followed by direct measurement in a PQ3 ICP-MS system (Thermo Electron Corporation, USA). The assay sequence was as follows: calibration standards of 0.2, 0.5, 1.0, 5.0, 10.0, 30.0, 60.0, 100.0 μg/L, volunteers' plasma samples and quality-control samples of 0.30, 8.00, 20.0, 80.00 μg/L throughout all sequences.

The two assay methods were validated according to international guidelines[21].

Chromatography

Chromatography for ranitidine was performed on a Beckman SYSTEM GOLD® liquid chromatography system (USA) consisting of a 125 solvent module, 508 auto-sampler, 166 UV detector and AT-330 column oven (Medilab). The software package 32 Karat 5.0 was used to control the chromatographic system and produce UV-spectrometric data. Analytical column used was Kromasil C18 ODS (Sweden, 250×4.6 mm ID, 5 μm, particle size), protected by a security guard cartridge C18 ODS 4×3.0 mm ID (Phenomenex Inc, USA). The mobile phase consisted of 0.02 mol/L KH_2PO_4-acetonitrile (86:14, V/V). The flow rate was 1.0 mL/min. Column oven was kept at 25 ℃. Auto-sampler was set at 4 ℃. The UV detective wavelength was 320 nm.

Working condition of ICP-MS

ICP-MS measurements were carried out under the following operation conditions. The forward power was 1350 W, the coolant and auxiliary and nebulizer gas

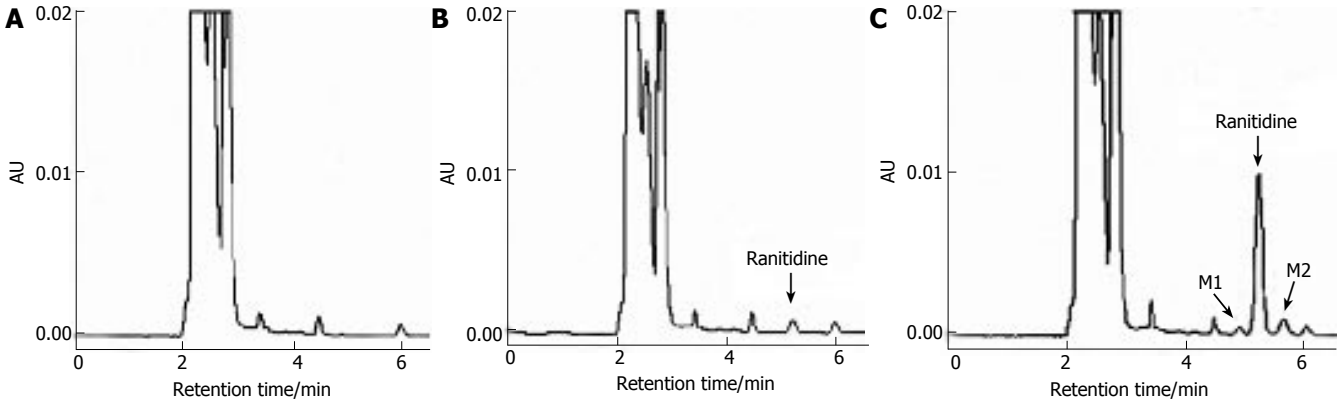

Figure 1 Chromatograms of spiked plasma sample (**B**), plasma samples of patients before (**A**) and after (**C**) the administration of 200 mg ranitidine. M1 and M2 are metabolites of ranitidine.

flow rate were 13, 0.70, and 0.73 L/min, respectively. Sample uptake flow rate was 1.2 mL/min. Mass-to-charge ratios detected (m/z) were 205 (^{205}Tl) and 209 (^{209}Bi). Sweep mode was peak hopping. Dwell time was 10 ms. Number of sweeps per run was 60. Uptake time was 60 s. Acquisition duration was 4 s.

Statistical analysis

Pharmacokinetic parameters were calculated by non-compartmental method. Bioequivalence evaluation was performed by the software BAPP2.0 (Center of Drug Metabolism & Pharmacokinetics, China Pharmaceutical University, Nanjing, China). Maximal plasma concentrations (C_{max}) and the time points at which they occurred (T_{max}) were determined by inspection of the plasma concentration-time profile. The terminal elimination rate constant (λ_z) was determined by linear regression of the terminal portion of the log concentration-time profile. The elimination half-life ($T_{1/2}$) was calculated as $0.693/\lambda_z$. Area under the plasma concentration-time curve (AUC) was determined by trapezoidal rule and extrapolated to infinity by calculation of C_t/λ_z. F=[$AUC_{(0\text{-}t)}$ (T)/$AUC_{(0\text{-}t)}$ (R)]×100%. Log transformed C_{max}, $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}\infty)}$ were analyzed using ANOVA analysis and Schuirmann two-one sided t-test. T_{max} was analyzed by the non-parametric test and Wilcoxon's test. A P value of less than 0.05 was considered statistically significant. Data were reported as mean ± SD. If the two preparations were bioequivalent, 90% confidence intervals (CI) for test/reference ratios of C_{max}, $AUC_{(0\text{-}t)}$ and $AUC_{(0\text{-}\infty)}$ should fall within the range of 80%-125% [22, 23].

RESULTS

Validation of the assays

Typical chromatograms of spiked ranitidine plasma samples, plasma samples of patients before and after the administration of compound ranitidine preparation are shown in Figure 1. The retention time for ranitidine was 5.1 min. Under the chromatographic condition described, ranitidine and its metabolite were well resolved. Endogenous plasma components did not show any interfering peaks. The assay was linear from 20.0 to 2000.0 μg/L for ranitidine in plasma samples. The mean absolute recovery was about 97.2%, while the intra- and inter-day coefficients of variation and percent error values of the assay method were all lower than 8%. The limit of quantification (LOQ) was found to be 20.0 μg/L, with a precision of less than 20% (n=5) and an accuracy of ±20% (n=5). Ranitidine was stable in plasma samples at different storage conditions: immediately after 3 h at ambient temperature, after perchloric acid treatment and being on the auto-sampler at 4 ℃ for 24 h, after two freeze/thaw cycles and after 1 mo storage at -80 ℃.

Table 1 Pharmacokinetic parameters of ranitidine and bismuth after a single oral dose of compound ranitidine preparation (equivalent to 200 mg of ranitidine and 220 mg of bismuth) in 20 Chinese volunteers (mean ± SD)

Component	Parameters	Test	Reference
Ranitidine	T_{max} (h)	2.3±0.9	2.1±0.9
	C_{max} (mg/L)	0.67±0.21	0.68±0.22
	$T_{1/2}$ (h)	2.8±0.3	3.1±0.4
	$AUC_{(0\text{-}t)}$ (mg/L per hour)	3.1±0.6	3.0±0.7
	$AUC_{(0\text{-}\infty)}$ (mg/L per hour)	3.3±0.6	3.2±0.8
Bismuth	T_{max} (h)	0.50±0.20	0.50±0.20
	C_{max} (μg/L)	11.80±7.36	11.40±6.55
	$T_{1/2}$ (h)	10.2±2.3	13.0±6.9
	$AUC_{(0\text{-}t)}$ (μg/L per hour)	46.65±16.97	47.03±21.49
	$AUC_{(0\text{-}\infty)}$ (μg/L per hour)	55.38±21.27	57.81±23.31

The ICP-MS assay was linear from 0.2-100.0 μg/L for bismuth in plasma samples. The mean absolute recovery of bismuth from quality control samples was about 100.5%, while the intra- and inter-day coefficients of variation and percent error values of the assay method were all lower than 8%. LOQ was found to be 0.2 μg/L, with a precision of less than 10% (n=30) and an accuracy of ±15% (n=30).

The validity study demonstrated that the HPLC assay was reliable for quantification of plasma ranitidine and the ICP-MS assay was reliable for determination of plasma bismuth levels. The specificity, sensitivity, accuracy and precision all met the requirement for PK study.

Concentration-time curves and PK of ranitidine

The average concentration-time curves are shown in Figure 2. The main PK parameters including C_{max}, $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}\infty)}$, T_{max} and $T_{1/2}$ are given in Table 1. The variation

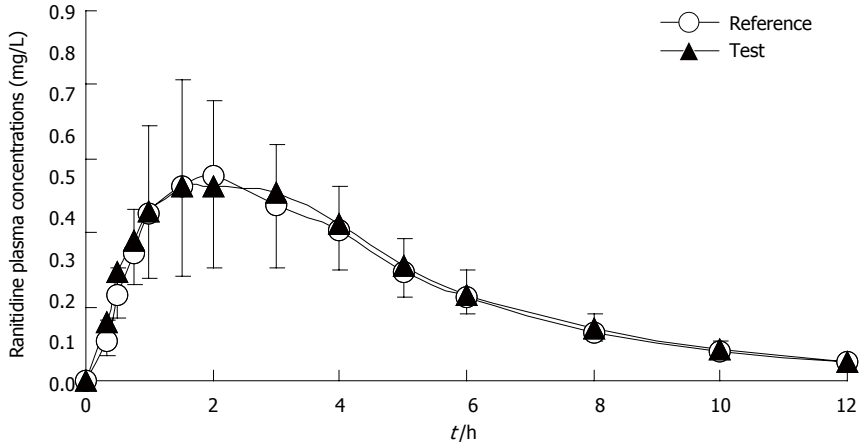

Figure 2 Concentration-time curves of ranitidine in 20 Chinese volunteers after oral administration of two compound preparations. $n = 20$. Mean ± SD. Bars indicate standard deviations (lower bars for test drug and upper bars for reference drug).

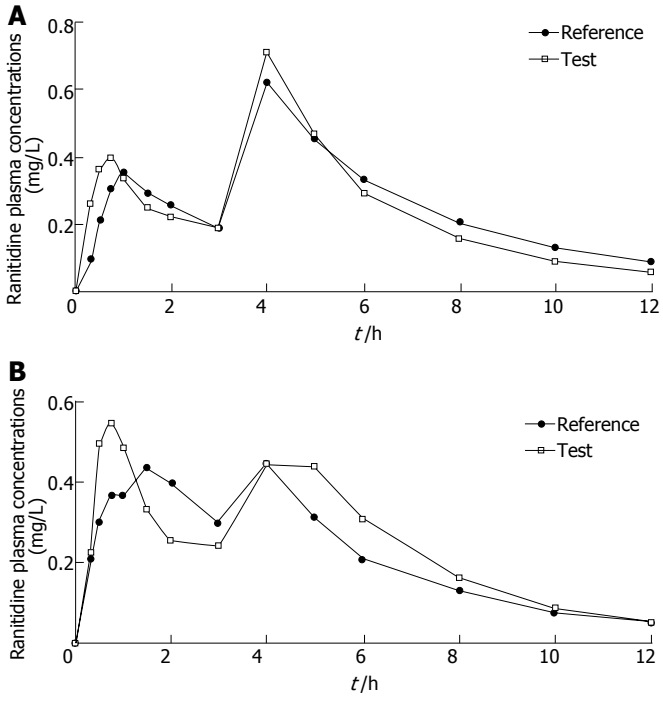

Figure 3 Typical double-peak plasma profiles of ranitidine in two Chinese volunteers (№14 and №16) after oral administration of two compound preparations.

sources of *P* values and 90% CI for the parameter ratios are presented in Table 2. No statistically significant formulation or period effect was encountered, with *P* value greater than 0.05. Inter-subject differences were the main source of variability in log-transformed $AUC_{(0\text{-}t)}$ and $AUC_{(0\text{-}\infty)}$. The 90% CI for the ratio of C_{max} (86.7%-113.6%), $AUC_{(0\text{-}t)}$ (96.0%-113.4%), and $AUC_{(0\text{-}\infty)}$ (95.3%-112.5%) values for the test and reference products was entirely within the FDA acceptable range of 80%-125%. The data indicated that the 2 preparations were bioequivalent with respect to ranitidine. In addition, no significant difference was obtained in T_{max}.

Interestingly, double-peak plasma profiles of ranitidine were observed in some volunteers receiving either test drug or reference drug. Typical double-peak plasma profiles of ranitidine in two volunteers (№ 14 and № 16) after oral administration of two compound preparations are shown in Figure 3.

Table 2 ANOVA for assessment of the drugs, subjects and period effects, and 90% CI for the test/reference ratio of C_{max}, $AUC_{(0\text{-}t)}$ and $AUC_{(0\text{-}\infty)}$, using logarithmic transformed data, after administration of two compound ranitidine preparations (equivalent to 200 mg of ranitidine and 220 mg of bismuth) to 20 Chinese volunteers ($\alpha = 0.05$).

Component	Parameters	ANOVA (*P*-value)			90% CI (%)
		Variation source			
		Drug	Subjects	Period	
Ranitidine	C_{max}	0.9191	0.0686	0.7679	86.7-113.6
	$AUC_{(0\text{-}t)}$	0.3917	0.0153	0.8366	96.0-113.4
	$AUC_{(0\text{-}\infty)}$	0.4733	0.02118	0.9064	95.3-112.5
Bismuth	C_{max}	0.65695	0.51515	0.39551	89.8-120.0
	$AUC_{(0\text{-}t)}$	0.66066	0.11347	0.71245	88.1-124.0
	$AUC_{(0\text{-}\infty)}$	0.75149	0.15804	0.87169	85.3-111.5

Concentration-time curves and PK of bismuth

The average concentration-time curves are shown in Figure 4. The main PK parameters including C_{max}, $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}\infty)}$, T_{max} and $T_{1/2}$ are given in Table 1. The variation sources of *P* values and 90% CI for the parameter ratios are presented in Table 2. No statistically significant formulation or period effect and inter-subject differences were encountered, with *P* value greater than 0.05. The 90% CI for the ratio of C_{max} (89.8%-120.0%), $AUC_{(0\text{-}t)}$ (88.1%-124.0%), and $AUC_{(0\text{-}\infty)}$ (85.3%-111.5%) values for the test and reference products was also entirely within the FDA acceptable range of 80%-125%. In addition, no significant difference was obtained in T_{max} ($P > 0.05$).

Safety

The two preparations were well tolerated by the volunteers. Unexpected incidents that could have influenced the outcome of the study did not occur. There was no drop-out and all volunteers participating in the study continued to the end. Post-study clinical laboratory tests revealed normal results.

DISCUSSION

The assay methods we developed for ranitidine and bismuth are reliable and applicable in bioavailability study. With respect to HPLC assay for ranitidine, direct

injection of the plasma samples after deproteination using perchloric acid warranted high sensitivity, good accuracy and precision and least time for sample preparation. Most literature on ranitidine determination in plasma involves solid-phase extraction (SPE)[24-26] or liquid-liquid extraction (LLE)[27-29]. However, the methods employing LLE not only consume large time for sample preparation but also give highly variable and relatively low recoveries. The SPE techniques are quite good, but they still involve several steps and need several hundred cartridges. With respect to the ICP-MS assay we developed for bismuth, sample preparation method is more simple and has less matrix effect than the method provided by Mauras Y *et al*[30].

The PK of ranitidine derived from ranitidine bismuth citrate is consistent with observations for ranitidine administered alone[31]. However, literature on PK of ranitidine derived from compound preparation is not yet available. Wen *et al*[32] showed that. C_{max} and $AUC_{(0-\infty)}$ derived from a single 300 mg dose of ranitidine alone are 0.91 mg/L and 4.78 mg/L per hour, respectively. However, when 300 mg colloidal bismuth sub-citrate capsules are co-administered, the two parameter values are significantly decreased by 41.8% and 33.7%, respectively. No significant differences have been observed with respect to T_{max} and $T_{1/2}$ under the two different circumstances, suggesting that ranitidine granules are partially enwrapped by colloidal precipitation as presented by Wen *et al*[32], which can explain the loss in ranitidine absorption. Ranitidine is characterized by a dose-proportional PK. So C_{max} and $AUC_{(0-\infty)}$ for ranitidine mono-preparations are both standardized to dose (200 mg), ranging 0.60-1.20 mg/L and 3.0-4.5 mg/L per hour, respectively[16-19,33]. The mean C_{max} and $AUC_{(0-\infty)}$ values for ranitidine derived from combined formulation in our study were 0.67 mg/L and 3.1 mg/L per hour, respectively, falling within the above range for ranitidine administered alone. If significant loss exists at absorption phase of ranitidine derived from test compound formulation and the decreased percentage is similar with the results of Wen *et al*[32]. C_{max} and $AUC_{(0-\infty)}$ values for ranitidine mono-preparation would be estimated to be 1.15 mg/L and 4.7 mg/L per hour, respectively, still being within/or near the mean range. Thus, the possible effects of bismuth potassium citrate on ranitidine absorption could not be excluded, thus more relative studies are needed to confirm the results presented by Wen *et al*[32]. Moreover, it would be useful to investigate the difference between the bioavailability of ranitidine in the compound preparation relative to the administration of two mono-preparations that are ingested simultaneously, although compound preparation has advantages such as more convenience in administration and better medication compliance in ulcer patients. However, the main purpose of this study was to confirm whether the two compound preparations can be prescribed interchangeably by bioequivalence evaluation.

The PK of oral drugs exhibiting double peaks cannot be adequately described by conventional compartmental models[34]. So we used non-compartmental method. The double-peak phenomenon of ranitidine plasma profile in several volunteers is consistent with previous reports[34,35,38]. However, this PK profile has not been revealed in Chinese. The proposal mechanism responsible for the existence of secondary peaks, presented by Yin *et al*[34] and Schaiquevich *et al*[35], includes enterohepatic recirculation and the existence of multiple sites of absorption along the gastrointestinal tract.

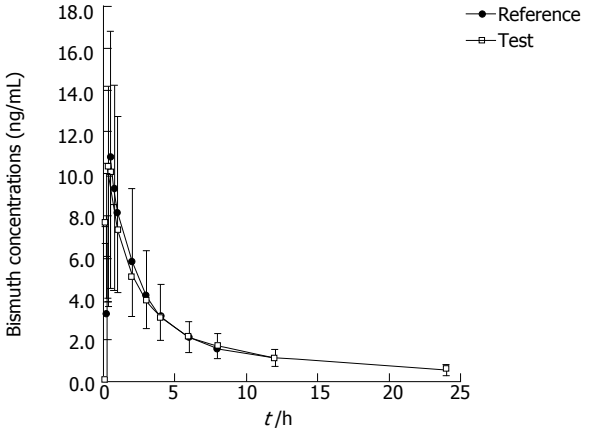

Figure 4 Concentration-time curves of bismuth in 20 Chinese volunteers after oral administration of two compound preparations. $n = 20$, mean ± SD. Bars indicate standard deviations (lower bars for test drug and upper bars for reference drug).

The mean T_{max} value for bismuth derived from compound preparations in this study was 0.50 h, indicating that bismuth is rapidly absorbed by Chinese volunteers. The result is similar with those presented by Nwokolo *et al*[13] and Benet *et al*[14]. Peak bismuth plasma concentrations in our study ranged 3.24 μg/L-27.50 μg/ L, the mean C_{max} value was 11.60 μg/L, suggesting that bismuth neurotoxicity is not associated with steady-state concentrations of 50-100 μg/L. The mean terminal half-lives for bismuth derived from the test compound preparation (equivalent to 220 mg bismuth) in this study was 10.2 h, which is nearly similar with the mean values of 9.1 h derived from a single dose of 350 mg ranitidine bismuth citrate capsules for 10 Chinese health volunteers[36]. Benet *et al*[14] considered that the intermediate half-life of 5-11 d derived from colloidal bismuth sub-citrate represents most of the clearance and elimination. Moreover, the plasma terminal half-lives averaging 21 d are derived from oral doses of 800 mg ranitidine bismuth citrate, twice daily for 28 d[31]. These different results are suggestive of possible ethnic differences in bismuth elimination or indicate that multiple-dose administration of bismuth may result in its prolonged elimination. In this way, further investigations should be carried out.

A placebo-controlled crossover study showed that daily oral administration of 40 mg omeprazole for 1 wk increases the systemic availability of 240 mg bismuth derived from tripotassium dicitrate bismuthate. The explanation by Treiber *et al*[37] is that absorption of bismuth may be dependent on intragastric pH which is elevated by omeprazole. However, the mean $AUC_{(0-t)}$ of bismuth derived from test compound preparation (equivalent to 200 mg of ranitidine and 220 mg of bismuth) in our study was 46.65 μg/L per hour, which is nearly similar with the value of 46 μg/L per hour derived from mono-preparation of tripotassium dicitrate bismuthate (equivalent to 220 mg of bismuth)[37]. Thus, additional experiments are also

needed to address whether ranitidine increases the systemic availability of bismuth.

The most important objective of bioequivalence testing is to assure the safety and efficacy of generic formulations. Two drugs are considered to be bioequivalent and thus therapeutically equivalent if they are pharmaceutical equivalents (i.e., similar dosage forms made, perhaps by different manufacturers) or pharmaceutical alternatives (i.e., different dosage forms) and if their rates (C_{max}) and extents of absorption (AUC) do not show a significant difference when administered at the same molar dose of the therapeutic moiety under similar experimental conditions[39]. Interpretation of T_{max} is difficult in some oral bioequivalence studies, because of the occurrence of multiple peaks. Comparison between the formulations is based on the overall C_{max}, T_{max}, and AUC. Therefore, the presence or absence of a double peak can not affect the accuracy of measurements[40].

It is generally accepted that the standard equivalence range is 0.8-1.25 for basic pharmacokinetic characteristics, such as AUC and C_{max}[22,23]. For ranitidine derived from the two compound preparations in this study, no significant difference was obtained in T_{max} ($P>0.05$) and 90% CI for the test/reference ratio of C_{max}, $AUC_{(0\text{-}t)}$ and $AUC_{(0\text{-}\infty)}$ was found within the range 80%-125%. Therefore the two compound preparations can be expected to be equally effective with respect to the action of ranitidine. To support equal clinical efficacy of compound preparations, it is necessary to show the equivalent gastric availability (local effect) of the bismuth component. Its effect for a large part is determined by the pharmaceutical form in which this component is delivered. Coghill *et al*[20] have developed a novel means of comparing the bioequivalence of the two preparations of tripotassium dicitrate bismuthate (De-Noltab) in patients attending a gastroscopy clinic by examining duodenal biopsies with electron microscopy. However, this method is invasive, thus lacking applicability. We performed a comparative bioavailability study to reflect the equal gastric availability indirectly. The results have confirmed the equivalent rates and extents of absorption of bismuth derived from the two compound preparations. Thus, we consider that these two compound preparations have equal clinical efficacy with respect to bismuth.

In conclusion, the 2 compound preparations are bioequivalent with respect to both ranitidine and bismuth and can be prescribed interchangeably.

REFERENCES

1 **Hoogerwerf WA,** Pasricha PJ. Agents used for control of gastric acidity and treatment of peptic ulcers and gastroesophageal reflux disease In: Hardman JG, Limbird LE, Goodman Gilman A, ed. The Pharmacological Basis of Therapeutics. New York: McGraw-Hill, 2001: 1005-1020

2 **Higuchi K,** Watanabe T, Tominaga K, Shiba M, Nakagawa K, Uno H, Kitada K, Satoh H, Chono S, Uchida T, Fujiwara Y, Arakawa T. Effects of ranitidine on quality of gastric ulcer healing compared with famotidine: a randomized, controlled, multicenter trial. *Int J Clin Pharmacol Res* 2005; **25:** 187-194

3 **Wu HS,** Lin SZ, Li YY, Du GG. Therapeutic effects of bismuth potassium citrate capsules on peptic ulcer and Helicobacter pylori infection. *Xin Yixue* 1992; **23:** 295-296

4 **Tytgat GN.** Colloidal bismuth subcitrate in peptic ulcer--a review. *Digestion* 1987; **37** Suppl 2: 31-41

5 **Lambert JR,** Midolo P. The actions of bismuth in the treatment of Helicobacter pylori infection. *Aliment Pharmacol Ther* 1997; **11** Suppl 1: 27-33

6 **Karateev AE,** Nasonov EL, Radenska-Lopovok SG. Efficacy of colloid bismuth subcitrate (De-Nol) in gastropathies induced by nonsteroid anti-inflammatory drugs: an open controlled 4-week trial. *Ter Arkh* 2005; **77:** 46-49

7 **Hu BR,** fen XL, Nie SF, Xiang JZ. Study of complex ranitidine on three ulcer models. *Acta Univ Med Tongji* 1999; **28:** 173-174

8 **Vondracek TG.** Ranitidine bismuth citrate in the treatment of Helicobacter pylori infection and duodenal ulcer. *Ann Pharmacother* 1998; **32:** 672-679

9 **Grant SM,** Langtry HD, Brogden RN. Ranitidine. An updated review of its pharmacodynamic and pharmacokinetic properties and therapeutic use in peptic ulcer disease and other allied diseases. *Drugs* 1989; **37:** 801-870

10 **Perez-Guille G,** Guille-Perez A, Toledo-Lopez A, Juarez-Olguin H, Flores Perez C, Flores-Prez J, Carrasco-Portugal M, Lares-Asseff I, Camacho-Vieyra A. Effect of age on the pharmacokinetics of ranitidine in healthy Mexican volunteers. *Proc West Pharmacol Soc* 2005; **48:** 84-88

11 **Flores Perez J,** Juarez Olguin H, Flores Perez C, Perez Guille G, Guille Perez A, Camacho Vieyra A, Toledo Lopez A, Carrasco Portugal M, Lares Asseff I. Effects of gender and phase of the menstrual cycle on the kinetics of ranitidine in healthy volunteers. *Chronobiol Int* 2003; **20:** 485-494

12 **Chung WG,** Park CS, Roh HK, Lee WK, Cha YN. Oxidation of ranitidine by isozymes of flavin-containing monooxygenase and cytochrome P450. *Jpn J Pharmacol* 2000; **84:** 213-220

13 **Nwokolo CU,** Gavey CJ, Smith JT, Pounder RE. The absorption of bismuth from oral doses of tripotassium dicitrato bismuthate. *Aliment Pharmacol Ther* 1989; **3:** 29-39

14 **Benet LZ.** Safety and pharmacokinetics: colloidal bismuth subcitrate. *Scand J Gastroenterol* 1991; **185 Suppl:** 29-35

15 **Slikkerveer A,** de Wolff FA. Pharmacokinetics and toxicity of bismuth compounds. *Med Toxicol Adverse Drug Exp* 1989; **4:** 303-323

16 **James LP,** Stowe CD, Farrar HC, Menendez AA, Argao EA. The pharmacokinetics of oral ranitidine in children and adolescents with cystic fibrosis. *J Clin Pharmacol* 1999; **39:** 1242-1247

17 **Li HL,** Gao SY, Jin O, Ying GZ. Bioequivalence of ranitidine hydrochloride effervescent granules in healthy volunteers. *Yaowu Fenxi Zazhi* 2001; **21:** 434-436

18 **Fu Q,** Xu XW, Mei D, Li DK. Bioequivalence of oral ranitidine from different pharmaceutical manufactures. *Zhongguo Yaoxue Zazhi* 1996; **31:** 288-290

19 **Bawazir SA,** Gouda MW, El-Sayed YM, Al-Khamis KI, Al-Yamani MJ, Niazy EM, Al-Rashood KA. Comparative bioavailability of two tablet formulations of ranitidine hydrochloride in healthy volunteers. *Int J Clin Pharmacol Ther* 1998; **36:** 270-274

20 **Coghill SB,** Shepherd AN. A novel means of comparing the bioequivalence of two formulations of tripotassium dicitrato bismuthate (De-Noltab). *Postgrad Med J* 1988; **64:** 761-763

21 **Shah VP,** Midha KK, Dighe S, McGilveray IJ, Skelly JP, Yacobi A, Layloff T, Viswanathan CT, Cook CE, McDowall RD. Analytical methods validation: bioavailability, bioequivalence and pharmacokinetic studies. Conference report. *Eur J Drug Metab Pharmacokinet* 1991; **16:** 249-255

22 **FDA**. Guidance on statistical procedures for bioequivalence studies using a standard two-treatment crossover design. Division of Bioequivalence, office of generic drugs, center for drug evaluation research, food and drug administration, Rockville, Maryland, 1992

23 **Chen ML,** Patnaik R, Hauck WW, Schuirmann DJ, Hyslop T, Williams R. An individual bioequivalence criterion: regulatory considerations. *Stat Med* 2000; **19:** 2821-2842

24 **Castro A,** Arancibia A, Romero P, Gai MN. Validated HPLC method for the determination of ranitidine in plasma. *Pharmazie* 2003; **58:** 696-698

25 **Hare LG,** Millership JS, Collier PS, McElnay JC, Carson DJ, Shields MS. The use of polymeric solid phase extraction and HPLC analysis for the determination of ranitidine in routine plasma samples obtained from paediatric patients. *J Pharm Pharmacol* 2001; **53:** 1265-1272

26 **Zendelovska D,** Stafilov T. Development of an HPLC method for the determination of ranitidine and cimetidine in human plasma following SPE. *J Pharm Biomed Anal* 2003; **33:** 165-173

27 **Wong CF,** Peh KK, Yuen KH. Simple high-performance liquid chromatographic method for the determination of ranitidine in human plasma. *J Chromatogr B Biomed Sci Appl* 1998; **718:** 205-210

28 **Flores Perez C,** Juarez Olguin H, Flores Perez J, Toledo Lopez A, Lares Asseff I, Alvarez Garcia C. Reliable method for the determination of ranitidine by liquid chromatography using a microvolume of plasma. *J Chromatogr B Analyt Technol Biomed Life Sci* 2003; **795:** 141-144

29 **Prueksaritanont T,** Sittichai N, Prueksaritanont S, Vongsaroj R. Simultaneous determination of ranitidine and its metabolites in human plasma and urine by high-performance liquid chromatography. *J Chromatogr* 1989; **490:** 175-185

30 **Mauras Y,** Premel-Cabic A, Berre S, Allain P. Simultaneous determination of lead, bismuth and thallium in plasma and urine by inductively coupled plasma mass spectrometry. *Clin Chim Acta* 1993; **218:** 201-205

31 **Koch KM,** Kerr BM, Gooding AE, Davis IM. Pharmacokinetics of bismuth and ranitidine following multiple doses of ranitidine bismuth citrate. *Br J Clin Pharmacol* 1996; **42:** 207-211

32 **Wen XK,** Yan Y, Zhong SL. Effects of coadministered colloidal bismuth subcitrate on pharmacokinetics of ranitidine in human volunteers. *Nanhua Daxue Xubao Yixue Ban* 2004; **32:** 176-177

33 **Flores-Murrieta FJ,** Toledo A, del Carmen Carrasco-Portugal M, Reyes-Garcia G, Rodriguez-Silverio J, Medina-Santillan R, Herrera JE. Comparative bioavailability of two oral formulations of ranitidine. *Biopharm Drug Dispos* 2006; **27:** 23-27

34 **Yin OQ,** Tomlinson B, Chow AH, Chow MS. A modified two-portion absorption model to describe double-peak absorption profiles of ranitidine. *Clin Pharmacokinet* 2003; **42:** 179-192

35 **Schaiquevich P,** Niselman A, Rubio M. Comparison of two compartmental models for describing ranitidine's plasmatic profiles. *Pharmacol Res* 2002; **45:** 399-405

36 **Jiang J,** Hu P, Xie HH. Pharmacokinetic Study of Bismuth in Chinese Health Volunteers. *Zhongguo Linchuang Yaoli Zazhi* 2000; **16:** 118-121

37 **Treiber G,** Walker S, Klotz U. Omeprazole-induced increase in the absorption of bismuth from tripotassium dicitrato bismuthate. *Clin Pharmacol Ther* 1994; **55:** 486-491

38 **Garg DC,** Weidler DJ, Eshelman FN. Ranitidine bioavailability and kinetics in normal male subjects. *Clin Pharmacol Ther* 1983; **33:** 445-452

39 **Chow SC,** Liu JP. Design and Analysis of Bioavailability and Bioequivalence Studies. New York: Marcel Dekker, 2000

40 **Suttle AB,** Pollack GM, Brouwer KL. Use of a pharmacokinetic model incorporating discontinuous gastrointestinal absorption to examine the occurrence of double peaks in oral concentration-time profiles. *Pharm Res* 1992; **9:** 350-356

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