



RAPID COMMUNICATION

Pharmacodynamic and kinetic effect of rabeprazole on serum gastrin level in relation to CYP2C19 polymorphism in Chinese Hans

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Abstract

AIM: To observe the pharmacokinetics and pharmacodynamics of rabeprazole and compare serum gastrin concentrations in different CYP2C19 genotype groups.

METHODS: The CYP2C19 genotype status of Chinese Han healthy volunteers was determined by polymerase chain reaction-restriction fragment length polymorphism method. Twenty *H. pylori*-negative healthy subjects voluntarily participated in the study. They were divided into the following three groups: homozygous extensive metabolizers (homEM), heterozygous extensive metabolizers (hetEM) and poor metabolizers (PM). After they orally received rabeprazole 20 mg once daily in the morning of d 1 and d 8, blood samples were collected at various time-points until 24 h after administration and intragastric pH values were monitored for 24 h by Digitrapper pH. Serum gastrin concentrations were measured by radioimmunoassay. Serum concentrations of rabeprazole were measured by high performance liquid chromatography.

RESULTS: The mean AUC values for rabeprazole after a single and repeated doses were significantly different between the homEM and PM groups, but not between the homEM and hetEM, or the hetEM and PM groups. No significant differences in intragastric pH medians were observed among the three different genotype groups after a single dose or repeated doses. The ratio of pH medians between d 1 and d 8 ranged from 84% to 108%. The mean gastrin AUC values were also different among the three genotype groups, with a relative ratio of 1.0, 1.2 and 1.5 after a single dose and 1.0, 1.5 and 1.6 after repeated doses in the homEM, hetEM and PM

groups, respectively. The gastrin AUC values among the three different genotype groups showed no significant difference either after a single dose or repeated doses. The subject who had lower intragastric acidity showed higher serum gastrin levels and concentrations of rabeprazole.

CONCLUSION: In Chinese Han healthy people, the pharmacokinetics of rabeprazole are dependent on the CYP2C19 genotype status, but acid-inhibitory efficacy of rabeprazole and the gastrin level are not influenced significantly.

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Key words: CYP450; Pharmacokinetics; Pharmacodynamics; Proton pump inhibitors

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INTRODUCTION

CYP450 2C19 is a genetically determined enzyme. Its phenotypes are either poor metabolizer (PM) or extensive metabolizer (EM)^[1,2] in the general population. When CYP2C19 is the main metabolism enzyme of a drug, the pharmacokinetics and pharmacodynamics of the drug are different between PMs and EMs. Rabeprazole (RPZ), a kind of the newer proton pump inhibitors (PPIs), has been reported to be metabolized mainly *via* a non-enzymatic pathway, with only minor CYP2C19 and CYP3A4 involvement. The pharmacokinetics of RPZ are expected to be less influenced by the CYP2C19 phenotype than those of omeprazole^[3-6]. However, it is not clear whether the pharmacokinetics and pharmacodynamics of RPZ depend on the CYP2C19 genotype status in Chinese Han people. On the other hand, it is well known that gastrin is secreted from G cells in the antrum of the stomach^[7], and an inhibition of gastric acid secretion by PPIs can stimulate gastrin release from G cells^[8]. Until now, little is known about the kinetics and pharmacodynamic effect

of RPZ on gastrin levels with respect to the polymorphic CYP2C19 in Chinese Han people. Therefore, in the present study, we observed the metabolic characteristics and pharmacodynamics of RPZ and serum gastrin levels after the single and 8-d repeated doses in the different CYP2C19 genotype groups. It showed that acid-inhibitory efficacy of rabeprazole and the gastrin levels were not influenced significantly by CYP2C19 genotype.

MATERIALS AND METHODS

Subjects and CYP2C19 genotypes

Twenty healthy male subjects who were negative for *H. pylori* infection were enrolled in the study. None of the subjects consumed alcohol or smoked, and none had taken any drugs at least 4 wk before or during the study. The protocol was approved in advance by the ethic committee of Anhui Medical University. Written informed consent was obtained from each of the subjects before participation in the study.

Genomic DNA was extracted from leucocytes of each individual using a commercially available kit (Promega, USA). The genotyping of CYP2C19, including CYP2C19*wt, CYP2C19*m1 and CYP2C19*m2, was performed by polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP)^[9]. The age of the subjects ranged from 20 to 23 years and body weight from 57 to 63 kg. Subjects were genotypically classified into the following three groups: homozygous extensive metabolizer group (homEM, $n = 7$), heterozygous extensive metabolizer group (hetEM, Wt/m1, $n = 4$; Wt/m2, $n = 2$) and poor metabolizer group (PM, m1/m1, $n = 7$).

Study protocol

Subjects were initially screened for *H. pylori* infection by a serological test (Dot-immunogold kit, Lanbo Bio-Tech Institute, China) and ¹³C-urea breath test. Each healthy volunteer received 20 mg RPZ (Pariet, Eisai Co. Ltd, Tokyo, Japan) orally for 8 d. The medications were taken once daily at 8:00 am. The 24-h intragastric pH monitoring and the measurement of plasma concentration of RPZ and gastrin level were performed on d 1 and d 8. Blood samples were collected before and 0.5, 1, 1.5, 2, 3, 5, 7, 10, 12, 24 h after administration on d 1 and d 8. After collection, the blood samples were immediately centrifuged at 4000 r/min for 10 min. One hundred microliter 1% diethylamine solution was added to the 1 mL plasma sample for determination of the concentration of RPZ. All samples were stored at -80°C until assayed. Plasma levels of RPZ were measured by high performance liquid chromatography^[10,11]. Serum gastrin levels were measured using radioimmunoassay (Gastrin-RIA kit, North Bio-Tech Institute, China).

Intragastric pH measurement

After overnight fasting, a glass electrode was inserted transnasally and placed about 5 cm below the cardia. The electrode was calibrated with standard buffers (pH 1.07 and 7.01) before recording the pH with a Digitrappher pH (Medtronic). Intragastric pH recordings started after the oral dose of RPZ at 8:00 am on d 1 and d 8. Two standard

Table 1 AUC of RPZ 20 mg after a single and repeated doses

	AUC ^a (μg/L per h) d 1	AUC ^a (μg/L per h) d 8
homEM	1150.24 ± 327.34	1445.28 ± 205.16
hetEM	1539.42 ± 190.29	1640.91 ± 249.51
PM	2015.38 ± 588.88	2495.61 ± 738.61

^a $P < 0.05$ homEM vs PM.

meals (noon, 18:00 pm), prepared at the hospital, were provided for each subject.

Pharmacokinetic analysis

Pharmacokinetic analysis was performed in a model-independent manner, and non-compartmental kinetic parameters (AUC) were calculated with 3P87 software. The area under concentration-time curve (AUC) for RPZ and gastrin in serum was shown from zero to 24 h (AUC₀₋₂₄).

Statistical analysis

The data are given as mean ± SD in all analyses. Differences in AUC and intragastric pH values between three genotype groups were compared using one-way analysis of variance (ANOVA) combined with the least significant method (LSD). To determine whether the gastrin concentrations and AUC values were increased from a single dose to repeated doses, the paired *t*-test was used. Statistical calculations were performed by SPSS 10.0 software. *P* value of less than 0.05 was considered to be statistically significant.

RESULTS

CYP2C19 genotype and AUC of RPZ

The mean AUC of RPZ is shown in Table 1. The mean AUC values for RPZ after a single dose differed among the three genotype groups, with a relative ratio of 1.0, 1.3 and 1.8 in the homEM, hetEM and PM groups, respectively. The mean AUC values for RPZ after repeated doses also differed among the three groups, with a relative ratio of 1.0, 1.1 and 1.7 in the homEM, hetEM and PM groups, respectively. The mean AUC values for RPZ after a single and repeated doses were significantly different between the homEM and PM groups, but not between the homEM and hetEM, or hetEM and PM groups. No significant change in the mean AUC values for RPZ from a single dose to repeated doses was observed in any of the three genotype groups.

CYP2C19 genotype and 24-h intragastric pH

The median intragastric pH value of the PM group was the highest, followed by that of the hetEM group, with that of the homEM group being the lowest (Table 2). No significant differences in intragastric pH values were observed among the three groups after a single dose and repeated doses of RPZ for 8 d. No significant changes in intragastric pH values from single to repeated doses were observed in the three genotype groups. The ratio of intragastric pH median after a single dose and that after repeated doses ranged from 84.5% to 107.4%, indicating that the metabolism of RPZ after a single dose could

Table 2 Median (interquartile range) 24 h pH after a single and repeated doses of RPZ 20 mg

	HomEM	HetEM	PM
D 1	3.82 (2.1-5.2)	4.36 (2.0-6.1)	6.09 (4.9-6.8)
D 8	4.52 (3.0-5.5)	4.37 (2.9-6.0)	5.67 (4.8-6.5)
D 1/D 8 (%)	84.5	99.8	107.4

Table 3 Serum gastrin level with reference to CYP2C19 polymorphism

	HomEM		HetEM		PM	
	D 1	D 8	D 1	D 8	D 1	D 8
Gastrin AUC	812.03 ± 1169.98 ±	964.08 ± 1771.38 ±	1181.06 ± 1897.45 ±			
(pg/mL per h) ^a	147.02	333.70	377.20	1024.90	420.70	1359.59

^aP < 0.05, AUC on d 1 vs AUC on d 8.

attain maximum acid-inhibitory efficacy.

CYP2C19 genotype and serum gastrin level

The 24-h mean serum gastrin concentration-time profiles are given in Figure 1. The mean serum gastrin concentration in PMs was significantly higher during all time periods than that in EMs. The mean serum gastrin AUC values in hetEMs observed after a single and repeated doses were between that of homEMs and PMs. The mean gastrin AUC values differed between the three genotype groups, with a relative ratio of 1.0, 1.2 and 1.5 after a single dose and 1.0, 1.5 and 1.6 after repeated doses in the homEM, hetEM and PM groups, respectively (Table 3). The gastrin AUC values among the three genotype groups showed no significant differences after a single dose and repeated doses of RPZ 20 mg. Significant increments in gastrin AUC values from a single dose to repeated doses were observed in the three different genotype groups.

As shown in Tables 1, 2 and 3, the subjects who had the lowest intragastric acidity showed the highest serum gastrin levels and the concentrations of RPZ.

DISCUSSION

PPIs, such as omeprazole and rabeprazole, have been used widely in the treatment of acid-related diseases. Studies have found that CYP2C19 is a major enzyme for the metabolism of PPIs in the liver^[12], and the inhibitory effects of PPIs are associated with the genotype of CYP2C19. The *in-vitro* human liver microsomal and *in-vivo* human pharmacology studies have shown that the metabolic profile of RPZ differs somewhat from other PPIs. RPZ is metabolized mainly *via* a nonenzymatic reduction to rabeprazole thioether^[12-14], and CYP2C19 and CYP3A4 are partially involved in the metabolism of RPZ^[12-14]. In addition, it has been shown that RPZ has a more rapid and powerful onset of pharmacological action^[15]. Yasuda^[10] found that the AUC for RPZ is not significantly increased after repeated doses. Our results showed that the AUC for RPZ after a single dose exceeded 80 percent of that after

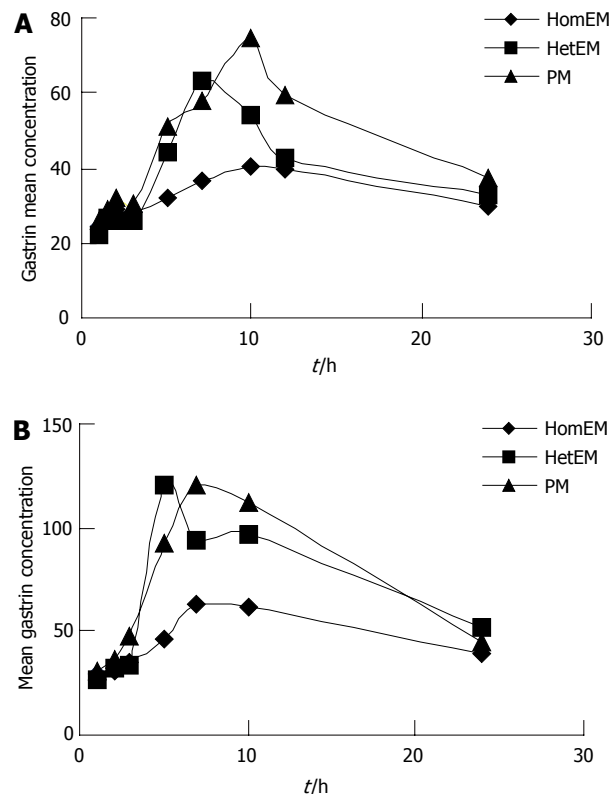


Figure 1 Mean serum gastrin concentration-time curve after a single dose (A) and repeated doses (B) of rabeprazole 20 mg.

repeated doses, and the gastric pH values after a single dose reached 84.5 to 107.4 percent of those after repeated doses. These findings suggest that the human body could absorb RPZ well, and RPZ could attain better acid-inhibitory efficacy.

Horai^[16,17] reported that CYP2C19 genotypic differences affect metabolism and pharmacokinetics of RPZ, and influence the gastric pH values and gastrin level in plasma. However, the majority of researchers^[3-6] believe that the acid-inhibitory efficacy and metabolism of RPZ are not dependent on the CYP2C19 genotype status. In our study, the acid-inhibitory efficacy and the gastrin level of rabeprazole were not influenced. This is supposed to be related with the small sample size of our study, as the number of subjects enrolled in each group was small. Ieiri^[18] reported that the mean AUC values for rabeprazole differed among the three genotype groups, with a relative ratio of 1.0, 1.7 and 3.8 in the homEM, hetEM and PM groups, being significantly related with genotype status. However, we found the AUC for RPZ was different markedly only between homEMs and PMs. Moreover, the intragastric pH, the best or most direct pharmacological index when using PPIs, had no significant differences among the three genotype groups after a single dose. After repeated doses of RPZ, the intragastric pH and AUC for RPZ were not affected by the CYP2C19 genotype status either. As for the discrepancy between the pharmacokinetics and pharmacodynamics of RPZ, we hypothesized that the acid inhibitory effect of RPZ was powerful and rapid, even in the homEM group.

When a PPI inhibits acid secretion, plasma or serum gastrin levels will be increased according to the degree

of acid inhibition, and serum gastrin concentration correlates well with gastric acid suppression^[19]. Therefore, plasma or serum gastrin concentration could be viewed as an indirect marker of the pharmacodynamic effects^[20]. Ieiri^[18] reported that the intergenotypic difference in the gastrin AUC was seen after the first dose of RPZ, and the AUC of serum gastrin on d 8 differed significantly between homEMs and PMs. However, in our study, no significant difference in the mean gastrin AUC was observed among the three genotype groups on d 1 and d 8, nor were significant differences in the median gastric pH levels found. We presume that the intergenotypic difference in serum gastrin AUC was synchronized with that in median gastric pH, which are consistent with the findings by Furuta^[8]. Previous studies indicated that serum gastrin concentrations returned to normal shortly after the antisecretory treatment with RPZ was discontinued^[21,22]; however, this phenomenon seems to be in conflict with the longlasting action of PPIs^[23]. Therefore, serum gastrin concentrations might not accurately reflect PPI-induced changes in intragastric pH, when PPIs were used in the different CYP2C19 genotype groups.

In conclusion, our study investigated mainly the pharmacodynamic and pharmacokinetic effect of rabeprazole on serum gastrin levels in association with different CYP2C19 genotypes. The acid-inhibitory effects of RPZ are independent of the CYP2C19 genotype status as well as the pharmacokinetic characteristics in the human body. Although the median gastric pH by RPZ treatment is related with the serum gastrin level, there is no significant difference between the different CYP2C19 genotype groups. RPZ is not only an effective proton pump inhibitor for treating the acid-related disease, but also does not affect serum gastrin level in association with CYP2C19 genotype status.

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