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ARTICLE

Evaluation of the relationship between polymorphisms in *CYP2C19* and the single-dose pharmacokinetics of omeprazole in healthy Chinese volunteers: A multicenter study

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Abstract

The aim of this study was to evaluate the relationship between polymorphisms in CYP2C19 and the single-dose pharmacokinetics (PKs) of omeprazole in healthy Chinese volunteers. A 20 mg single dose of omeprazole (Losec) enteric-coated capsules or tablets was orally administered to 656 healthy subjects from eight subcenters. The polymorphic alleles of *CYP2C19**2, *3, and *17 were determined by Sanger sequencing and Agena mass array. Plasma concentrations of omeprazole were determined by high-performance liquid-chromatography tandem mass spectrometry. PK parameters of area under the concentration versus time curve $(AUC)_{0\text{-}t}$, AUC from zero to infinity ($AUC_{0\text{-}\infty}$), maximum plasma concentration (C_{max}), and terminal half-life ($t_{1/2}$) were significantly influenced by *CYP2C19* phenotype (all $p < 0.001$) and diplotype (all $p < 0.001$), and the same results were obtained in the subgroup analysis of the effects of diet and dosage form.

The polymorphisms of *CYP2C19*2*(rs4244285; all PK parameters $p < 0.001$) and **3*(rs4986893; $p_{Cmax} = 0.020$, and the p values of other PK parameters were less than 0.001) were significantly associated with the PKs of omeprazole. For *CYP2C19**17 (rs12248560), only $t_{1/2}$ showed a significant correlation ($p = 0.032$), whereas other PK parameters did not. The present study demonstrated that the Pks of omeprazole is greatly influenced by *CYP2C19*.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

CYP2C19 is involved in the drug's metabolism and that poor metabolizers have a greater systemic exposure to omeprazole followed by intermediate and then extensive metabolizers.

WHAT QUESTION DID THIS STUDY ADDRESS?

This study aimed to examine the effect of *CYP2C19* polymorphisms on the pharmacokinetics parameters of omeprazole in healthy Chinese volunteers after a single dose by a large sample multicenter study.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

The present study demonstrated that the pharmacokinetics (AUC_{0-t}, $AUC_{0-\infty}$, C_{max} and $t_{1/2}$) of omeprazole is greatly influenced by *CYP2C19* (rs4244285, rs4986893 and rs1224856).

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

In the clinical application of omeprazole, attention should be paid to the effect of *CYP2C19* polymorphisms. If necessary, the clinical therapeutic dose of omeprazole should be guided base on the results of *CYP2C19* gene test.

INTRODUCTION

The commonly prescribed proton-pump inhibitor (PPIs) omeprazole is the first-line treatment against acid-related diseases, such as gastric and duodenal ulcers, gastroesophageal reflux disease, nonerosive reflux disease, and Zollinger–Ellison syndrome.[1] Omeprazole is extensively metabolized by the liver P450 cytochrome enzyme *CYP2C19*, whose second metabolic pathway is CYP3A4. Therefore, polymorphisms in *CYP2C19* may affect the pharmacokinetics (PKs) of omeprazole.[2,3] Due to differences in hepatic enzyme activity, the PKs of omeprazole show extensive interindividual variability that may lead to poor predictability of treatment-related outcomes and adverse effects.[4] Therefore, this study was conducted to evaluate the effect of CYP2C19 on the PKs of omeprazole in healthy Chinese volunteers.

Among more than 20 *CYP2C19* described alleles, the most frequent ones are *CYP2C19**2 (rs4244285, 681 G>A) and *CYP2C19**3 (rs4986893, 636 G>A), which encode nonfunctional proteins,[5,6] whereas *CYP2C19**17 (rs12248560, −806 C>T) has been associated with increased metabolic activity.[7,8] Individuals could be classed into four phenotypes according to the *CYP2C19* genotype, as follows: *CYP2C19* normal metabolizers (NMs) are characterized by the presence of two normal function alleles (*CYP2C19* *1/*1); *CYP2C19* intermediate metabolizers (Ims) are characterized by the presence of one normal function allele, and one no function allele (*CYP2C19* *1/*2 and *CYP2C19* *1/*3), or one no function allele and one increased function allele (*CYP2C19* *2/*17 and *CYP2C19* *3/*17); *CYP2C19* poor metabolizers (PMs) are characterized by the presence of two no function alleles (*CYP2C19* *2/*2, *CYP2C19* *3/*3, and *CYP2C19* *2/*3); diplotypes, which are characterized by one normal function allele and one increased function allele (*CYP2C19* *1/*17), are classified as rapid metabolizers (RMs).[9] Previous studies have shown that the area under the concentration versus time curve (AUC) for PPIs is higher in Ims and PMs and lower in ultra metabolizers (UMs) than in extensive metabolizers (EMs) of *CYP2C19* polymorphisms in White patients.[10] Compared with African Americans (4%) and Whites (3%), the proportion of PMs in Chinese subjects is very high (17.4–35.0%).[11,12] The contribution of CYP2C19 polymorphism to PK differences after omeprazole administration in Chinese has been mentioned before,[13-15] but

the sample size of these studies was small (18–27 cases), and the subjects included in each single-center study were not representative enough. Therefore, a multicenter study with a larger sample size of Chinese people is needed to validate these findings.

The US Food and Drug Administration (FDA)-approved drug label for omeprazole (PRILOSEC) notes that *CYP2C19* is involved in the drug's metabolism and that PMs have a greater systemic exposure to omeprazole followed by Ims and then EMs.[16] Moreover, the drug labels in Canada, Japan, and Switzerland contain information about the change in efficacy, dosage, and metabolism due to phenotypes.[17] Meanwhile, the Clinical Pharmacogenetics Implementation Consortium (CPIC)[18] and Royal Dutch Pharmacists Association – Pharmacogenetics Working Group (DPWG)[19] have evaluated therapeutic dose recommendations for omeprazole based on *CYP2C19* genotype. Patients who are *CYP2C19* UMs should receive an increased (about 3-fold higher) dose. However, more data and clinical evidence are needed to update the above treatment recommendations and compensate for the missing data in the Chinese population.

The present study aimed to examine the effect of *CYP2C19* polymorphisms on the PK parameters of omeprazole in healthy Chinese volunteers after a single dose.

MATERIALS AND METHODS

Study design and subjects

Our study population included 656 healthy Chinese adult volunteers from eight single-dose bioequivalence clinical trials of omeprazole. In each original bioequivalence study, blood samples were collected during the period during which the subjects first took the reference preparation Losec and PK parameters AUC versus time curve (AUC_{0-t}), AUC from zero to infinity ($AUC_{0-\infty}$), maximum plasma concentration (C_{max}), time to C_{max} (T_{max}), and terminal half-life ($t_{1/2}$) were calculated. The sample size, dosage, dietary status, blood sample collection time, and PK parameters of each bioequivalence clinical trial are listed in Table 1.

All subjects were found to be healthy on the basis of their physical examination, medical history, vital signs (blood pressure, pulse rate, and temperature), laboratory tests (blood chemistry, hematology, and urine analysis), and 12-lead electrocardiogram. Furthermore, the volunteers were not allowed to take drugs or medications during the study periods.

All these bioequivalence clinical trials were performed in hospitals of China between 2018 and 2020. Our study protocol was approved by the Ethics Committee of Peking University First Hospital as the leading center (No. 2018(21)) and the Ethics Committees of each bioequivalence clinical trials' hospital. Informed written consent was obtained from each subject. The present study was registered at the Chinese Clinical Trial Registry, with a registration number of No. ChiCTR1800016231.

Each subject received a single dose of omeprazole (Losec) with a glass of tap water. Venous blood samples were collected for analysis before dosing and at different times after drug administration. The samples were centrifuged at 1700–3000 g and 4°C, 10 mins after collection, and stored at less than or equal to 60°C.

Genotyping of *CYP2C19* polymorphism

The gene detection methods included Sanger sequencing and Agena mass array. The Sanger sequencing process included DNA extraction, polymerase chain reaction (PCR) amplification, and sequencing by ABI3730 analyzer. Agena mass array single-nucleotide polymorphism (SNP) detection, which was performed according to the manufacturer's protocol, included PCR cycling program, shrimp alkaline phosphatase digestion, and single-base extension. Then, extension products were desalted and detected using matrix-assisted laser desorption ionization time-of-flight. Finally, the results were analyzed using TYPER 4.0 software (Agena Bioscience, San Diego, CA). The SNPs, primer sets, and probe sequences that were used in the above assay are shown in Table S1.

Allele frequencies for the variant SNPs were assessed for deviation from Hardy-Weinberg equilibrium using the chi-square test.[20] According to the hypothesis testing theory, the alpha value of the acceptance test should be higher or at least not lower than the alpha value of the refusal test. By convention, the value of α was determined as 0.05 in our study. The SNP loci that were in Hardy-Weinberg equilibrium were further analyzed for PK-pharmacogenetics (PGx) correlation.

Determination of plasma concentrations and pharmacokinetics analysis

Plasma concentrations of omeprazole (sum of both enantiomers) were determined by ultra-high-performance liquid chromatography-tandem mass spectrometry. The noncompartmental method of Phoenix WinNonlin (Pharsight Co., Mountain View, CA) was used for the analysis of PK parameters.

The C_{max} and the T_{max} were directly estimated from the observed plasma concentration-time data. PK parameters determined after a single dose included the $AUC_{0-\infty}$) and

TABLE 1 Overview of subcenter

No.	Subcenter name	Dietary status	Sample size	Blood sample collection time	No. of blood samples	PK parameters
Enteric Capsules, 20 mg						
1	Jiangsu Province Hospital of Chinese Medicine	Fasting	50	0 h, 0.5 h, 0.75 h, 1 h, 1.25 h, 1.5 h, 1.75 h, 2 h, 2.5 h, 3 h, 3.5 h, 4 h, 4.5 h, 5 h, 6 h, 7 h, 8 h, 10 h, 12 h, 24 h	20	AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, $t_{1/2}$
		Fed	50	0 h, 0.75 h, 1 h, 1.5 h, 2 h, 2.5 h, 3 h, 3.5 h, 4 h, 4.5 h, 5 h, 5.5 h, 6 h, 7 h, 8 h, 10 h, 12 h, 14 h, 24 h	19	
2	The Third Xiangya Hospital of Central South University	Fasting	82	0 h, 2 h, 2.5 h, 3 h, 3.5 h, 4 h, 4.5 h, 5 h, 5.5 h, 6 h, 6.5 h, 7 h, 7.5 h, 8 h, 9 h, 10 h, 12 h, 14 h	18	AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, $t_{1/2}$
		Fed	95	0 h, 2 h, 2.5 h, 3 h, 3.5 h, 4 h, 4.5 h, 5 h, 5.5 h, 6 h, 6.5 h, 7 h, 7.5 h, 8 h, 9 h, 10 h, 12 h, 14 h, 16 h, 24 h[b]	20	
3	Shanghai Public Health Clinical Central	Fed	39	0 h, 0.25 h, 0.5 h, 1 h, 1.5 h, 2 h, 2.5 h, 3 h, 3.5 h, 4 h, 4.5 h, 5 h, 5.5 h, 6 h, 6.5 h, 7 h, 7.5 h, 8 h, 10 h, 12 h, 16 h, 24 h	24	AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, $t_{1/2}$
4	Wuxi People's Hospital	Fed	58	0 h, 1 h, 1.5 h, 2 h, 2.5 h, 3 h, 3.5 h, 4 h, 4.5 h, 5 h, 5.5 h, 6 h, 7 h, 8 h, 9 h, 10 h, 12 h, 14 h, 16 h	19	AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max},
5	Wuhan Jinyintan Hospital	Fed	42	0 h, 0.5 h, 1 h, 1.5 h, 2 h, 2.5 h, 3 h, 3.5 h, 4 h, 4.5 h, 5 h, 5.5 h, 6 h, 6.5 h, 7 h, 8 h, 9 h, 10 h, 12 h, 24 h	20	AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, $t_{1/2}$
6	Hebei Hospital of Traditional Chinese Medicine	Fasting	40	0 h, 0.25 h, 0.5 h, 0.75 h, 1 h, 1.25 h, 1.5 h, 1.75 h, 2 h, 2.25 h, 2.5 h, 2.75 h, 3 h, 3.33 h, 3.67 h, 4 h, 4.33 h, 4.67 h, 5 h, 5.5 h, 6 h, 8 h, 10 h, 12 h	24	AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, $t_{1/2}$
		Fed	37	0 h, 1 h, 2 h, 2.5 h, 3 h, 3.5 h, 4 h, 4.5 h, 5 h, 5.5 h, 6 h, 6.5 h, 7 h, 7.5 h, 8 h, 9 h, 10 h, 11 h, 12 h, 13 h, 14 h, 15 h, 16 h, 18 h	24	
Enteric tablets, 20 mg						
7	The Second Affiliated Hospital Zhejiang University School of Medicine	Fed	44	0 h, 0.5 h, 1 h, 1.5 h, 2 h, 2.5 h, 3 h, 3.5 h, 4 h, 4.5 h, 5 h, 6 h, 7 h, 8 h, 10 h, 12 h	16	AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, $t_{1/2}$
8	The Third Xiangya Hospital of Central South University[a]	Fasting	82	0 h, 0.5 h, 0.75 h, 1 h, 1.25 h, 1.5 h, 1.75 h, 2 h, 2.25 h, 2.5 h, 3 h, 3.5 h, 4 h, 4.5 h, 5 h, 6 h, 8 h, 10 h, 12 h	19	AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, $t_{1/2}$
		Fed	37	0 h, 1.5 h, 2 h, 2.5 h, 3 h, 3.5 h, 4 h, 4.5 h, 5 h, 5.5 h, 6 h, 6.5 h, 7 h, 7.5 h, 8 h, 10 h, 12 h, 14 h	18	

Abbreviations: AUC_{0-t}, area under the concentration versus time curve; $AUC_{0-\infty}$, AUC from zero to infinity; C_{max}, maximum plasma concentration; NA, not available; PK, pharmacokinetic; T_{max}, time to C_{max}; $t_{1/2}$, terminal half-life.

[a]The same subcenter, but another form.

[b]Forty-five cases did not collect blood samples of 16 h and 24 h.

$t_{1/2}$. Due to the different design of blood sampling points in the two subcenters, $AUC_{0\text{-}t}$ was not included in the PK-PG correlation study, and $AUC_{0\text{-}\infty}$ was used instead.

Statistical analysis

The PK-PG correlation analyses were performed using SPSS version 25.0 (SPSS, Chicago, IL). Subjects were grouped according to the detection results of a single SNP, genotypes, or metabolic phenotypes. The Mann-Whitney *U* test was used to evaluate the significance of differences in PK parameters between the two genotypic groups. Data from three or more different genotypic groups were compared using the Kruskal-Wallis H test. The significance of the differences in PK parameters (including C_{max}, T_{max}, $t_{1/2}$, T_{max} $AUC_{0\text{-}t}$, and $AUC_{0\text{-}\infty}$) among different SNPs, genotypes, and metabolic phenotypes were determined, and the subgroup analyses were performed according to dosage form and dietary status. Any p less than 0.05 was considered to be statistically significant.

RESULTS

CYP2C19 polymorphism distribution

The allele frequencies and genotype frequencies are shown in Table 2. The gene mutation frequencies of *CYP2C19**2 (rs4244285, 681G>A), *CYP2C19**3 (rs4986893, 636G>A), and *CYP2C19**17 (rs12248560, −806C>T) were 31.1%, 5.56%, and 0.84%, respectively. Hardy-Weinberg equilibrium test results showed that all the detected SNPs were in Hardy-Weinberg equilibrium ($p > 0.05$, Pearson test). The distributions of diplotype and phenotypic frequencies of *CYP2C19* are summarized in Table 3. The assignment of predicted *CYP2C19* phenotype based on genotype was referred to as CPIC guidance.[18]

TABLE 2 The frequencies of SNPs and results of the Hardy-Weinberg tests

SNP	Allele	Number of cases (%)	Genotype	Number of cases (%)	Pearson's P
*CYP2C19*2*	G	904 (68.9)	GG	322 (49.09)	0.054
	A	408 (31.1)	GA	260 (39.63)	
			AA	74 (11.28)	
*CYP2C19*3*	G	1239 (94.44)	GG	585 (89.18)	0.981
	A	73 (5.56)	GA	69 (10.52)	
			AA	2 (0.3)	
*CYP2C19*17*	C	1301 (99.16)	CC	645 (98.32)	0.829
	T	11 (0.84)	CT	11 (1.68)	

Abbreviation: SNPs, single-nucleotide polymorphisms.

TABLE 3 The distributions of diplotype and phenotypic frequencies of CYP2C19

Metabolic phenotypes	The definition of metabolic phenotypes	Sample size (*n*, %)	Diplotypes	Sample size (*n*, %)
RM	An individual carrying one normal function allele and one increased function allele	6 (0.91)	*1/*17	6 (0.91)
NM	An individual carrying two normal function alleles	263 (40.09)	*1/*1	263 (40.09)
IM	An individual carrying one normal function allele and one no function allele or one increased function allele and one no function allele	294 (44.82)	*1/*2	241 (36.74)
			*1/*3	48 (7.32)
			*2/*17	2 (0.30)
			*3/*17	3 (0.46)
PM	An individual carrying two no function alleles	93 (14.18)	*2/*2	74 (11.28)
			*2/*3	17 (2.59)
			*3/*3	2 (0.30)

Abbreviations: IM, intermediate metabolizer; NM, normal metabolizer; PM, poor metabolizer; RM, rapid metabolizer.

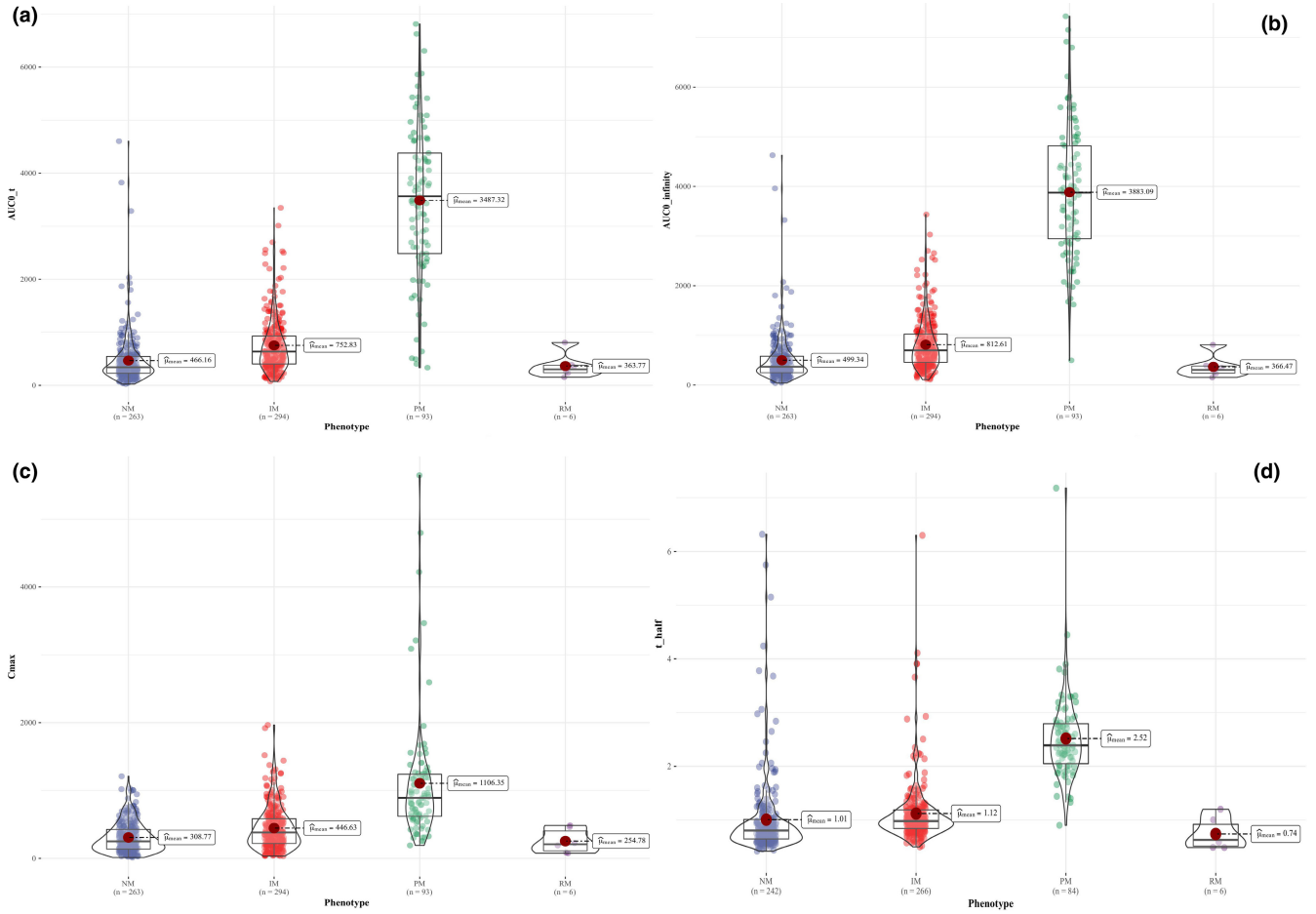

FIGURE 1 Scatter plot of omeprazole pharmacokinetic parameters according to diplotype (a) area under the concentration versus time curve ($AUC_{0\text{-}t}$), (b) AUC from zero to infinity ($AUC_{0\text{-}\infty}$), (c) maximum plasma concentration (C_{max}), (d) time to C_{max} (T_{max}), (e) terminal half-life ($t_{1/2}$)

Effect of *CYP2C19* polymorphism on pharmacokinetics

The differences of $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, C_{max}, and $t_{1/2}$ among GG, GA, and AA of *CYP2C19**2 (rs4244285) were significantly different (AUC0-t, AUC0-∞, C_{max}, and $t_{1/2}$ were all $p < 0.001$), whereas there was no statistically significant difference in T_{max} ($p = 0.092$). The relative $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, C_{max}, and $t_{1/2}$ value in the GG, GA, and AA were 1:1.86:6.47, 1:1.83:6.68, 1:1.48:3.40, and 1:1.18:2.46, respectively. The differences in $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, C_{max}, and $t_{1/2}$ among GG, GA, and AA of *CYP2C19**3 (rs4986893) were statistically significant ($pc_{max} = 0.02$, the other $p < 0.001$), whereas there was no statistically significant difference in T_{max} ($p = 0.998$). The relative $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, C_{max}, and $t_{1/2}$ value in the GG, GA, and AA were 1:1.55:4.09, 1:1.56:4.25, 1:1.25:1.88, and 1:1.18:2.32, respectively. For *CYP2C19**17 (rs12248560), compared with CC, only the reduction in $t_{1/2}$ was statistically significant in the CT group ($p = 0.032$), whereas the decreases in $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, C_{max}, and T_{max} were not statistically significant ($pAUC_{0\text{-}t} = 0.141$, $pAUC_{0\text{-}\infty} = 0.108$, $pC_{max} = 0.278$ and $pT_{max} = 0.135$). The mean (±SD) PK parameters of every SNP are summarized in Table S2.

The $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, C_{max}, and $t_{1/2}$ of nine diplotype groups were significantly different (all $p < 0.001$), but the T_{max} was not ($p = 0.098$), The difference was summarized in Figure 1. The relative $AUC_{0\text{-}\infty}$ values in the *1/*17, *1/*1, *3/*17, *2/*17, *1/*3, *1/*2, *2/*2, *2/*3, and *3/*3 were 0.73, 1, 1.10, 1.39, 1.62, 1.64, 7.59, 8.45, and 8.90, respectively. $AUC_{0\text{-}t}$, C_{max}, and $t_{1/2}$ also followed this trend. The T_{max} value was achieved at 1.33–4.60 h after administration in all subjects. The mean (±SD) PK parameters of omeprazole in the nine diplotype groups are summarized in Table 4 and the pairwise comparisons of each group are shown in Table S3. In the pairwise comparisons of $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, C_{max}, and $t_{1/2}$, *1/*2, *2/*2, *1/*3, and *2/*3 vs *1/*1, *2/*2 and *2/*3 vs *1/*2, *2/*2, and *2/*3 vs *1/*3, *2/*2, and *2/*3 vs *1/*17 were significantly different.

Compared with NM *CYP2C19* *1*1, the $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, C_{max}, and $t_{1/2}$ of IMs and PMs were significantly increased, whereas they were decreased in the RM group.

TABLE 4 Pharmacokinetic parameters of omeprazole (mean ± SD) according to *CYP2C19* diplotype

	*1/*1 (*n* = 263)	*1/*2 (*n* = 241)	*1/*3 (*n* = 48)	*1/*17 (*n* = 6)	*2/*3 (*n* = 17)	*2/*2 (*n* = 74)	*3/*17 (*n* = 3)	*2/*17 (*n* = 2)	*3*3 (n = 2)	*p* value
$AUC_{0\text{-}t}$, h*ng/ml	466.2 ± 493.2	766.4 ± 529.4	707.8 ± 490.3	363.8 ± 232.6	3908 ± 1560	3379 ± 1421	544.8 ± 14.52	507.3 ± 150.3	3913 ± 493.0	0.000*
$AUC_{0\text{-}\infty}$, h*ng/ml	499.3 ± 498.4	817.8 ± 524.4	808.0 ± 545.9	366.5 ± 233.4	4221 ± 1453	3790 ± 1311	547.0 ± 14.47	693.0 ± 109.6	4444 ± 793.4	0.000*
C_{max}, ng/ml	309 ± 227	449 ± 309	440 ± 390	255 ± 180	1040 ± 550	1130 ± 992	310 ± 129	530 ± 344	884 ± 575	0.000*
$t_{1/2}$, h	1.01 ± 0.76	1.12 ± 0.62	1.41 ± 0.71	0.74 ± 0.29	2.54 ± 0.70	2.51 ± 0.82	0.86 ± 0.13	0.90 ± 0.09	2.88	0.000*

Abbreviations: AUC, area under the curve; C_{max}, maximum plasma concentration; $t_{1/2}$, biological half-life; T_{max}, time to reach maximum plasma concentration.

*The difference was statistically significant ($p < 0.05$).

The difference is summarized in Figure 2. The relative $AUC_{0\text{-}t}$ value in the RM, NM, IM, and PM was 0.78, 1, 1.61, and 7.48, the relative $AUC_{0\text{-}\infty}$ value in the RM, NM, IM, and PM was 0.73, 1, 1.63, and 7.78, the relative C_{max} value in the RM, NM, IM, and PM was 0.83, 1, 1.45, and 3.58, and the relative $t_{1/2}$ value in the RM, NM, IM, and PM was 0.73, 1, 1.11, and 2.50, respectively. The T_{max} value was achieved at 3.89–4.45 h after administration in all groups. The PK parameters of omeprazole in the four phenotype groups are summarized in Table 5, and the pairwise comparisons of each group are shown in Table S3. In the pairwise comparisons, the $AUC_{0\text{-}\infty}$ of the PM group significantly differed from all other groups ($p_{PM\text{-}RM} < 0.001$, $p_{PM\text{-}NM} < 0.001$, and $p_{PM\text{-}IM} < 0.001$), and the IM and NM groups also significantly differed ($p_{IM\text{-}NM} < 0.001$).

Subgroup analysis of different dietary states

Of the 656 healthy subjects included in the study, 254 took omeprazole on an empty stomach (no food intake within 8 h), and 402 took omeprazole after a high-fat meal. The PK parameters between the fasted group and the fed group are shown in Table S4. The differences in PK parameters between the fasting and postprandial groups were significantly different. The same results were obtained in fasted and fed subgroups. There were statistically significant differences in $AUC_{0\text{-}t}$ ($p < 0.001$), $AUC_{0\text{-}\infty}$ ($p < 0.001$), C_{max} ($p < 0.001$), and $t_{1/2}$ ($p < 0.001$) among the different CYP2C19 phenotypes, whereas there were no statistically significant differences in T_{max} ($p_{fasted} = 0.553$ and $p_{fed} = 0.287$) among the different CYP2C19 phenotypes. The PK parameters of the different metabolic phenotypes in each subgroup are shown in Table S5.

Subgroup analysis of different drug dosage forms

Of the 656 healthy subjects, 537 were taking enteric-coated capsules, and 119 were taking enteric-coated tablets. The differences in PK parameters between the fasting and postprandial groups were significantly different (Table S4). The same results were obtained in enteric-coated capsules and tablets subgroups. There were statistically significant differences in $AUC_{0\text{-}t}$ ($p < 0.001$), $AUC_{0\text{-}\infty}$ ($p < 0.001$), C_{max} ($p < 0.001$), and $t_{1/2}$ ($p < 0.001$) among the different CYP2C19 phenotypes, but there was no significant difference in T_{max} ($p_{enteric\text{-}coated\ capsules} = 0.107$ and $p_{enteric\text{-}coated\ tablets} = 0.601$) among the different CYP2C19 phenotypes. The PK parameters of different metabolic phenotypes in each subgroup are shown in Table S6.

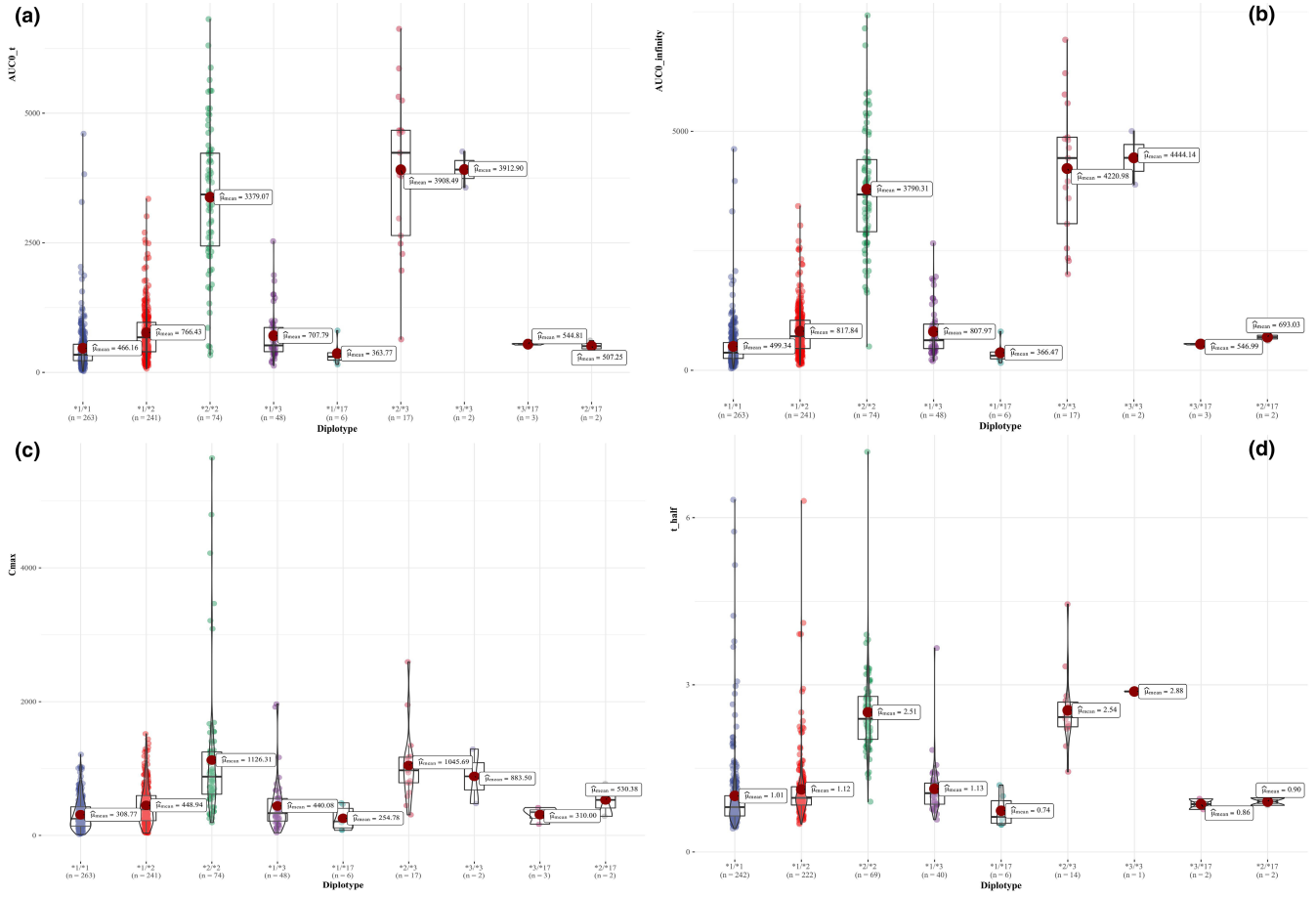

FIGURE 2 Scatter plot of omeprazole pharmacokinetic parameters according to phenotype (a) area under the concentration versus time curve ($AUC_{0\text{-}t}$), (b) AUC from zero to infinity ($AUC_{0\text{-}\infty}$), (c) maximum plasma concentration (C_{max}), (d) time to C_{max} (T_{max}), (e) terminal half-life ($t_{1/2}$)

TABLE 5 Pharmacokinetic parameters of omeprazole (mean ± SD) according to *CYP2C19* phenotype

	RM ($n = 6$)	NM ($n = 263$)	IM ($n = 294$)	PM ($n = 93$)	*p* value
$AUC_{0\text{-}t}$, h*ng/ml	363.77 ± 232.56	466.16 ± 493.21	519.18 ± 752.83	3487.32 ± 1440.13	0.000*
1331.02 $AUC_{0\text{-}\infty}$, h*ng/ml	366.47 ± 233.42	499.34 ± 498.44	812.61 ± 523.39	3883.09 ± 1331.02	0.000*
C_{max}, ng/ml	254 ± 180	308 ± 227	447 ± 322	1110 ± 916	0.000*
$t_{1/2}$, h	0.74 ± 0.29	1.01 ± 0.76	1.12 ± 0.60	2.52 ± 0.79	0.000*

Abbreviations: AUC, area under the curve; C_{max}, maximum plasma concentration; IM, intermediate metabolizer; NM, normal metabolizer; PM, poor metabolizer; RM, rapid metabolizer; $t_{1/2}$, biological half-life; T_{max}, time to reach maximum plasma concentration.

*The difference was statistically significant ($p < 0.05$).

DISCUSSION

In the present study, we found significant differences in the $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, C_{max}, and $t_{1/2}$ of omeprazole in healthy Chinese volunteers with different genotypes. This multicenter, large sample study examined the effect of *CYP2C19* polymorphisms on the PK parameters of omeprazole in healthy volunteers.

Herein, we investigated the correlation between PG and PK based on a bioequivalence study. The bioequivalence study of generic drugs has been widely carried out in China over recent years. There are multiple pharmaceutical companies conducting bioequivalence studies for generic drugs at the same stage. According to the policy requirements of China, the reference drugs for a bioequivalence study of generic drugs should be selected from the "Reference Listed Drug for Generic Drugs." For omeprazole in the present study, the generic reference drug from different manufacturers is Losec (AstraZeneca UK Limited). Herein, we used an opportunity to include the

bioequivalence study of omeprazole conducted across eight different pharmaceutical companies as a subcenter and successfully obtained a large sample size of 656 volunteers. To the best of our knowledge, this is the largest such study to date. This is an innovation in research methodology and organizational form with Chinese characteristics, which can verify the effect of gene polymorphisms on PKs in more subjects with lower cost, shorter time, and better quality. Conducting genetic polymorphism studies with healthy subjects has many advantages, such as controlling for confounding factors, like disease and drug interactions, reducing the effect of individual differences, and providing a more realistic and accurate correlation to PG and PK.

The *CYP2C19* phenotypes tend to differ in relation to race. Loss of *CYP2C19* *2, *CYP2C19* *3, and other functiona, which are responsible for PM alleles, is mainly found in Asians.[21] *CYP2C19* *2 has an allele frequency of 25–30% in Asians, about 15% in Europeans and Africans, and about 60% in Oceanians.[9,18] The allele frequency of *CYP2C19* *2 in our study is 31.1%, which is consistent with the 1000 Genomes and previous reports.[22] *CYP2C19* *3 has an allele frequency of about 15% in Oceanians, 0.04% in Whites,[22] and 2–7% in Asians,[9] which allele frequency is 5.56% in our study. The increased function allele *CYP2C19* *17 is most common in European, African, and Near Eastern populations, with an allele frequency of about 20%.[9,23] However, the allele frequency in our study of Chinese participants is only 0.84%. PM status has been found in 2.5–3.5% of Whites, 2% of American Blacks, and ~20% of Asians.[22] Of the 656 subjects enrolled in this study, the proportion of PM status was 11.59%. Therefore, it is still necessary to carry out a study with a large sample size in the Chinese population to clarify the correlation between omeprazole PK characteristics and *CYP2C19* in the Chinese population, regardless of previous studies conducted in other populations.

The classification of *CYP2C19* predicted phenotypes in this study was defined according to the latest CPIC guidelines.[9] Compared with the historical classification, the main change lies in the attribution of *1/*17. This classification is more scientific, detailed, and clear than the DPWG guidelines[23] and previous studies of the same type.[15]

Our results showed a statistically significant difference in the PK parameters $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, C_{max}, and $t_{1/2}$ of different *CYP2C19* metabolizers after oral administration of 20 mg omeprazole in healthy Chinese volunteers. These findings are consistent with previous studies that have reported on populations including European, Saharan, and Asian populations.[8,24–26] Of these, the most representative was the $AUC_{0\text{-}\infty}$ that reflects the extent of drug clearance, which was significantly increased in PM, 9.6, 7.5, and 6.5 times in RM, NM, and IM, respectively. This result, which is consistent with previous studies,[27] complements the relevant data of the NM group as well as more PK parameters. The C_{max} of the response drug efficacy and safety was also significantly increased in PM, 4.4-fold RM, 3.6-fold NM, and 2.5-fold IM, respectively. When grouped according to different genotypes, the $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, C_{max}, and $t_{1/2}$ were also significantly different, which is consistent with the results of a previous study in a White population.[7]

The present study has some limitations. First, the efficacy of omeprazole was not evaluated. As a drug that inhibits gastric acid secretion, this study failed to evaluate and analyze intragastric PH or symptom relief as an effective outcome for more clinical application value. Second, we obtained PK parameters rather than all plasma concentration test results, thus failing to visually show the concentration-time curve of different genotypes and broader the population-by-population PK modeling.

In conclusion, our study demonstrated that the PKs of omeprazole is greatly influenced by CYP2C19 in Chinese healthy subjects. In the clinical application of omeprazole, attention should be paid to the effect of CYP2C19 polymorphisms.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

S.Z., R.X., and X.Z. wrote the manuscript. Y.C., X.Z., and Q.X. designed the research. X.Z., X.H., J.H., J.Y., M.L., Y.D., D.Y., Y.L., Q.Z., G.Y., F.L., S.G., Q.H., H.L., F.G., and X.M. performed the research. S.Z., R.X., and Q.X. analyzed the data. Q.X. and Y.C. contributed new analytical tools.

REFERENCES

1. Shah N, Gossman W. Omeprazole. In *StatPearls* (StatPearls Publishing Copyright © 2021. StatPearls Publishing LLC; 2021.
2. Andersson T. Pharmacokinetics, metabolism and interactions of acid pump inhibitors. Focus on omeprazole, lansoprazole and pantoprazole. *Clin Pharmacokinet*. 1996;31:9-28.
3. Li XQ, Andersson TB, Ahlstrom M, Weidolf L. Comparison of inhibitory effects of the proton pump-inhibiting drugs omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole on human cytochrome P450 activities. *Drug Metab Dispos*. 2004;32:821-827.
4. El Rouby N, Lima JJ, Johnson JA. Proton pump inhibitors: from CYP2C19 pharmacogenetics to precision medicine. *Expert Opin Drug Metab Toxicol*. 2018;14:447-460.

5. Sagar M, Seensalu R, Tybring G, Dahl ML, Bertilsson L. CYP2C19 genotype and phenotype determined with omeprazole in patients with acid-related disorders with and without Helicobacter pylori infection. *Scand J Gastroenterol*. 1998;33:1034-1038.
6. Take S, Mizuno M, Ishiki K, et al. Interleukin-1beta genetic polymorphism influences the effect of cytochrome P 2C19 genotype on the cure rate of 1-week triple therapy for Helicobacter pylori infection. *Am J Gastroenterol*. 2003;98:2403-2408.
7. Román M, Ochoa D, Sánchez-Rojas SD, et al. Evaluation of the relationship between polymorphisms in CYP2C19 and the pharmacokinetics of omeprazole, pantoprazole and rabeprazole. *Pharmacogenomics*. 2014;15:1893-1901.
8. Sim SC, Risinger C, Dahl M, et al. A common novel CYP2C19 gene variant causes ultrarapid drug metabolism relevant for the drug response to proton pump inhibitors and antidepressants. *Clin Pharmacol Ther*. 2006;79:103-113.
9. Lima JJ, Thomas CD, Barbarino J, et al. Clinical pharmacogenetics implementation consortium (CPIC) guideline for CYP2C19 and proton pump inhibitor dosing. *Clin Pharmacol Ther*. 2021;109:1417-1423.
10. Hunfeld NG, Mathot RA, Touw DJ, et al. Effect of CYP2C19*2 and *17 mutations on pharmacodynamics and kinetics of proton pump inhibitors in Caucasians. *Br J Clin Pharmacol*. 2008;65:752-760.
11. Hu YM, Xu JM, Mei Q, Xu XH, Xu SY. Pharmacodynamic effects and kinetic disposition of rabeprazole in relation to CYP2C19 genotype in healthy Chinese subjects. *Acta Pharmacol Sin*. 2005;26:384-388.
12. Shu Y, Zhou HH. Individual and ethnic differences in CYP2C19 activity in Chinese populations. *Acta Pharmacol Sin*. 2000;21:193-199.
13. Yin OQ, Tomlinson B, Chow AH, Waye MM, Chow MS. Omeprazole as a CYP2C19 marker in Chinese subjects: assessment of its gene-dose effect and intrasubject variability. *J Clin Pharmacol*. 2004;44:582-589.
14. Qiao H, Hu Y-R, Tian X, et al. Pharmacokinetics of three proton pump inhibitors in Chinese subjects in relation to the CYP2C19 genotype. *Eur J Clin Pharmacol*. 2006;62:107-112.
15. Hu XP, Xu JM, Hu YM, Mei Q, Xu XH. Effects of CYP2C19 genetic polymorphism on the pharmacokinetics and pharmacodynamics of omeprazole in Chinese people. *J Clin Pharm Ther*. 2007;32:517-524.
16. US Food and Drug Administration (FDA). Drug Approval Package. Products on NDA 022056. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/022056_prilosec_toc.cfm#:~:text=Prilosec%20%28omeprazole%29%20for%20Delayed-Release%20Oral,Suspension%20Company%3A%20AstraZeneca%20Application%20No.%3A%20022056
17. PharmGKB. Omeprazole-Drug Label Annotations. 2021. https://www.pharmgkb.org/labelAnnotations
18. Lima JJ, Thomas CD, Barbarino J, et al. Clinical pharmacogenetics implementation consortium (CPIC) guideline for CYP2C19 and proton pump inhibitor dosing. *Clin Pharmacol Ther*. 2021;109:1417-1423.
19. PharmGKB. Annotation of DPWG Guideline for omeprazole and CYP2C19.
20. Namipashaki A, Razaghi-Moghadam Z, Ansari-Pour N. The essentiality of reporting Hardy-Weinberg equilibrium calculations in population-based genetic association studies. *Cell J*. 2015;17:187-192.
21. Harris DM, Stancampiano FF, Burton MC, et al. Use of pharmacogenomics to guide proton pump inhibitor therapy in clinical practice. *Dig Dis Sci*. 2021;66(12):4120-4127.
22. Yang J, Lin C. CYP2C19 genotypes in the pharmacokinetics/pharmacodynamics of proton pump inhibitor-based therapy of Helicobacter pylori infection. *Expert Opin Drug Metab Toxicol*. 2010;6:29-41.
23. Swen JJ, Nijenhuis M, de Boer A, et al. Pharmacogenetics: from bench to byte–an update of guidelines. *Clin Pharmacol Ther*. 2011;89:662-673.
24. Yasuda S, Horai Y, Tomono Y, et al. Comparison of the kinetic disposition and metabolism of E3810, a new proton pump inhibitor, and omeprazole in relation to S-mephenytoin 4′-hydroxylation status. *Clin Pharmacol Ther*. 1995;58:143-154.
25. Herrlin K, Massele AY, Jande M, et al. Bantu Tanzanians have a decreased capacity to metabolize omeprazole and mephenytoin in relation to their CYP2C19 genotype. *Clin Pharmacol Ther*. 1998;64:391-401.
26. Michaud V, Kreutz Y, Skaar T, et al. Efavirenz-mediated induction of omeprazole metabolism is CYP2C19 genotype dependent. *Pharmacogenomics J*. 2014;14:151-159.
27. Park S, Hyun YJ, Kim YR, et al. Effects of CYP2C19 genetic polymorphisms on PK/PD responses of omeprazole in Korean healthy volunteers. *J Korean Med Sci*. 2017;32:729-736.

SUPPORTING INFORMATION

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