Pharmacokinetics and Bioequivalence of Two Formulations of Omeprazole and Sodiun bicarbonate powder, for suspension: A Randomized, Single-Dose, Two-Period, Two-Sequence Crossover Study in Healthy Chinese Volunteers

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Article

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Abstract

Introduction: Omeprazole and sodium bicarbonate powder can effectively treatment for acid-related disorders. This study compared the bioequivalence of the two formulations of omeprazole and sodium bicarbonate powder and assessed how CYP2C19 gene polymorphisms affects pharmacokinetic (PK).

Methods: This study used a single-center, randomized, single-dose, 2-sequence, and 2-period crossover method, researched among forty healthy Chinese subjects. Blood sample were collected after a single-dose for PK (AUC0-∞, AUC0-t, and Cmax) analysis. The concentrations of Omeprazole in human plasma were determined by HPLC-MS/MS. Finally, the gene polymorphisms of CYP2C19 were assessed by Sanger sequencing.

Results: The geometric mean ratios (90% confidence interval) [GMR (95%CI)] of Test/Reference preparation for Cmax: 95.2% (88.48%, 102.43%), AUC0-t: 97.47% (94.4%,101.02%), AUC0-∞:97.68% (94.27%, 101.21%) were within the range of 80.00%-125.00%. Non-parametric test showed no statistical difference in Tmax between the two groups. (P>0.05). All drugs were well tolerated and no severe adverse reactions occurred, and there was also no significant differences in adverse events between the two drugs.

For CYP2C19 gene polymorphisms, the results showed that of 40 subjects, 12 subjects were extensive metabolizer (EM), 24 were intermediate metabolizer (IM) and 4 were poor metabolizer (PM). The results of PK parameters showed that different genotypes of CYP2C19 lead to significant differences in $t_{1/2}$, $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$ and C_{max}, but no significant differences in T_{max} in each group.

Conclusion: This study has shown that the pharmacokinetic parameters of the two formulations are not significantly different, which showed bioequivalence and good safety. CYP2C19 gene polymorphism has significant difference in PK parameters of omeprazole sodium bicarbonate suspension. It is suggested that attention should be paid to patients with poor metabolism in clinical application, and timely adjustment of drug delivery regimen should be made to avoid adverse reactions.

Introduction

Proton pump inhibitors (PPIs) are widely used to treat a variety of acid related disorders, including gastro esophageal reflux disease (GERD)[1], peptic ulcer disease(PUD)[2], Helicobacter pylori (H.pylori) infections[3], and the prophylaxis of stress- and NSAID-induced PUD[4–6]. Omeprazole (OME) has been widely recognized and used as the first generation of new acid inhibitors once discovered[7]. Omeprazole has been used in combination with antibiotics such as amoxicillin and clarithromycin to eradicate helicobacter pylori[8]. The main metabolic enzyme is CYP2C19, the secondary metabolic enzyme is CYP3A4 in the liver, factors affecting the activity of CYP2C19 include age[9], drugs, etc., which may also influence the metabolism of OME, causes changes in AUC and its activity. The abnormality of CYP2C19 coding gene is the most crucial and the most researched pharmacogenetic factor affecting OME response. There are many non-genetic factors can affect PPIs, but the variation caused by CYP2C19

genotype is important, it accounts for a large part of the PK variability of PPI[10]. PPIs were first completely metabolized by CYP450 in the hepar, of all, CYP2C19 genetic polymorphisms is the most important enzyme to metabolize the drugs[11]. Because of the different of the CYP2C19 gene polymorphisms, the subjects can be separated into three groups, extensive metabolizers (EM) intermediate metabolizers (IM) and poor metabolizers (PM)[12]. Of the CYP2C19 genetic polymorphisms, many studies found that due to variations in*2(G681A) and *3(G636A), the enzyme activity was reduced[13–15]. Compared with Caucasians, the frequency of CYP2C19 slow metabolizers in Asians is 13%-23%, which is much higher than that of Caucasians[16]. Due to the low CYP2C19 activity and slow drug clearance, the plasma exposure of PM is higher. Clinical efficacy will vary due to different blood drug concentrations. Thus, it is worth to notice the phenotyping of CYP2C19 revealed because according to reports, 2 single base pair mutations (CYP2C19*2 and *3) define more than 99% of the PM allele in Asian populations[17].

The pharmacological effect of omeprazole is mainly through the formation of a covalent complex with H+-K+-ATPase in the activated form of sulfonamide derivatives, which irreversibly inactivates the latter and blocks the final step of gastric acid secretion, and finally reaches acid suppression effect[18]. Till now, all available delayed-release PPIs are enteric-coated preparations that are administered orally including oral suspensions, disintegrating tablets and capsules, because its easily destroyed in stomach. Different intestinal coverings are necessary to protect unstable PPI from acid degradation in the stomach, but have the probable detriment of delaying absorption of PPI[19]. The FDA approved the American Santarus Company’s Omeprazole Sodium Bicarbonate Dry Suspension for the market in June 2004, the product name is "ZEGERID", and the indications are gastro esophageal reflux disease, active benign gastric ulcer, etc. A number of studies have confirmed this feature of omeprazole sodium bicarbonate preparations[20, 21]. A new immediate-release suspension of omeprazole is protected from stomach acid degradation by sodium bicarbonate. Sodium bicarbonate increases the pH in the stomach so that protects the omeprazole, facilitating its rapid absorption which in turn inhibits gastric acid secretion. Omeprazole can directly act on the proton pump channel to inhibit the secretion of gastric acid by the proton pump. Because the proton pump channel is activated more thoroughly, this allows the omeprazole sodium bicarbonate capsules to inhibit gastric acid for a longer time. This feature has great clinical value in the relief and continuous control of symptoms such as peptic ulcer, erosive esophagitis, GERD acid reflux, and heartburn. Large number of patients in China, generic drugs improves access to treatment. This study aims to compare the omeprazole sodium bicarbonate dry suspension produced by Harbin Meijun Pharmaceutical Co., Ltd. (trial preparation, specification: omeprazole 20mg + sodium bicarbonate 1680mg) and omeprazole sodium bicarbonate dry suspension produced by Santarus (Santarus) Company (reference preparation, trade name: ZEGERID) by using single-center, randomized, open, single-dose, two-cycle, two-sequence and double-crossover trials in Chinese healthy subjects. The bioequivalence of the two preparations was evaluated by the main pharmacokinetic parameters and relative bioavailability, so as to provide clinical basis for the drug registration application of the tested preparations. And in the Chinese population, the incidence of PM for CYP2C19 is high (17.4%)[22]. Thus, it is necessary to make it clear how the pharmacokinetics of this drug depend on the CYP2C19 genotype

status. Therefore, through this study, we will also compare the effects CYP2C19 gene polymorphisms on pharmacokinetic parameters.

Methods

Compliance with Ethics Guidelines.

This research was conducted under the guidance of the Declaration of Helsinki, Good Clinical Practice (GCP) guidelines of China Food and Drug Administration (CFDA) and authorized by the independent ethics committee of Tongji Medical College, Huazhong University of Science and Technology (No. (2018)186-1). Written informed consent from each volunteer is required before any procedure can proceed. Clinical trial registration numbers: ChiCTR2200058964. The date of registration is 20/04/2022.

Subjects.

This study included 40 subjects. The subjects were aged 18–65 years (including 18 and 65 years old),the male' s body weight ≥ 50.0 kg and for females ≥ 45.0 kg, the range of body mass index (BMI)from 19 to 26 kg/m2. All of them were good at communicating with investigators, and they can follow the requirements that contraception must be used at least 4 weeks before dosing, throughout the study period, and 90 days after study drug dosing. The exclusion criteria are as follows: history of any chronic disease; current or recent disease that could have influenced the pharmacokinetic (PK) parameters of this drug; smoking or alcohol addiction; use of prescription/ over-the-counter drugs within 14 days before taking the study drug; pregnant women; lactating women; subjects with a history of allergy to other benzimidazoles. Informed consent was obtained from all participants.

Study design.

This study was single dose and two-period PK/PD study which is shown in Fig. 1.

Forty subjects were randomly divided into two groups with 20 patients in each group. Give the drugs to the patients of each group in the order of T-R and R-T in the two cycles, with a single dose of 1 bag (each bag: 20mg omeprazole + 1680mg sodium bicarbonate). The subjects in each group fasted after 21:00 the night before administration. Collecting plasma samples at 0h (within 60min before administration) and after administration of 5min, 10min, 15min, 20min, 30min, 45min, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 10h, 12h (a total of 16 points) and stored at − 80℃ until analysis.

Analytic methods.

The concentration of omeprazole in EDTA-K2 anticoagulant human plasma was determined by HPLC-MS/MS. The omeprazole-D3 was quantified by internal standard (internal standard: omeprazole-D3).The sample pretreatment method was protein precipitation method. The linear range of omeprazole plasma concentration determination method was 4 ~ 4000 ng/mL, and the minimum quantitative limit was 4 ng/mL.

Pharmacokinetics analysis.

The pharmacokinetic (PK) parameters evaluated in this study included peak plasma omeprazole concentration (Cmax) and plasma peak concentration time (T_{max}) obtained directly from non-interpolated data, as well as the area under the plasma concentration curve of Omeprazole at 0-t after administration [AUC(0–t)] using the linear trapezoidal method to calculate. Terminal elimination rate constant λz and the apparent terminal elimination half-life (T½) were also needed. AUC0-∞ (the AUC from time 0 to infinity) used the formula: AUC0-∞=AUC0-t + Ct / λ(t1/2 0.693/λz) to calculate. The average plasma concentrations for each sampling time were also calculated.

Safety evaluations.

Safety was assessed by gathering electrocardiograms, vital signs, physical examination, and clinical laboratory results. AEs was divided into mild, moderate or severe, to determine the relationship between the study drug and AEs according to the criterions declared by the World Health Organization.

Statistical methods.

SAS 9.4 software was used for statistical analysis. After logarithmic conversion, C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ performed two-way unilateral t-test to calculate the 90% confidence interval of the geometric mean ratio of omeprazole C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ in the plasma of tested preparation T and reference preparation R. When the 90% confidence interval of the geometric mean ratio of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ between the tested preparation and the reference preparation is within the equivalent interval of 80.00%-125.00%, the bioequivalence of the two preparations can be determined. Besides, the T_{max} of test preparation T and reference preparation R were evaluated by nonparametric method.

Results

Subjects

A total forty volunteers (24 males and 16 females) were recruits. The mean age of this volunteers group was 24.24 ± 4.08 years. And the mean height and body weight were respectively 165.46 ± 7.91cm and 60.21 ± 7.97kg, with the mean BMI of 21.87 ± 1.76 kg/m^2. There were no statistically significant differences in age, height, mean body weight and BMI between the T-R group and R-T group.

Safety and tolerability.

Two formulations of Omeprazole and Sodium bicarbonate powder have safety and healthy volunteers were well tolerated throughout the trial. There were no significant changes in all data or information of physical examination, vital signs, laboratory examination results or 12 lead ECG compared with those before administration. In this study, a total of 12 subjects had 19 adverse events; the incidence rate was 30%. Of the 12 subjects, 9 belong to the IM group, 2 are PM, and 1 is EM. Among them, there were 1 case

of metabolic and nutritional diseases (1 case of hyperuricemia), 3 cases of infection and infection diseases (3 cases of upper respiratory tract infection), and 10 cases of various examinations (1 case of white blood cell count increased, 1 case of elevated alanine transfers, 1 case of urinary white blood cell positive, 2 cases of hemoglobin decrease, 2 cases of abnormal electrocardiogram T wave, 1 case of urine red blood cell positive, 1 case of blood pressure drop, platelet count decrease 1 case), 5 cases of gastrointestinal diseases (3 cases of abdominal distension, 1 case of nausea, 1 case of gastro esophageal reflux disease). Adverse events occurred in 11 cases in the T-R dosing sequence and 8 cases in the R-T dosing sequence. The severity of adverse events was mild in 11 cases and moderate in 1 case. Except for one subject with reduced hemoglobin who reported no discomfort and refused to come to the hospital for review, the other adverse events had improved or disappeared/relapsed after follow-up. Neither the reference reagent nor the test reagent had serious adverse reactions.

Pharmacokinetic Parameters

The pharmacokinetic parameters and pharmacokinetic curves of test drug and reference drug are listed below (Table 1, Fig. 2). After a single fasting oral administration of test or reference in 40 healthy subjects, the calculated AUC0-t of test and reference were (1530.61 ± 1584.30) ng·h/mL and (1553.81 ± 1618.30) ng•h/mL respectively, $AUC_{0-\infty}$ were (1572.21 ± 1642.10) ng·h/mL and (1594.10 ± 1676.30). The peak time (T_{max}) was (0.28 ± 0.11) h and (0.27 ± 0.15) h, and the peak concentration (C_{max}) was (981.50 ± 431.72) ng/mL and (1010.35 ± 430.97) ng/mL, respectively. And there were no statistically significant differences in the extent and rate of drug exposure between T preparation and R preparation.

Table 1
Summary of main pharmacokinetic parameters of two formulations of Omeprazole and sodium bicarbonate powder.

Parameter	**Arithmetic mean ± SD(%CV)(N = 40)**	
	Test Preparation	**Reference Preparation**
C_{max}(ng /mL)	981.50 ± 431.72(43.99)	1010.35 ± 430.97(42.66)
T_{max}(h)	0.25(0.17, 0.75)	0.25(0.08, 1.00)
AUC0-t(ng•h/mL)	1530.61 ± 1584.30(103.51)	1553.81 ± 1618.30(104.15)
AUC0-∞(ng•h/mL)	1572.21 ± 1642.10(104.45)	1594.10 ± 1676.30(105.16)
T1/2(h)	1.15 ± 0.71(61.77)	1.15 ± 0.68(59.05)
λz(1/h)	0.774 ± 0.308(39.839)	0.759 ± 0.290(38.193)
Note: AUC0 t = AUC from time 0 (baseline) to time t; AUC0-∞= AUC from baseline to infinity. *No significant between-treatment differences were found.		

Bioequivalence.

As summarized in Table 2, compare test and reference preparation, the GMR of Cmax,AUC_{0-t} and $AUC_{0-\infty}$ were 95.20 97.47 97.68 respectively, and the 90% CIs ranged from 88.48 ~ 102.43 94.04 ~ 101.02 and 94.27 ~ 101.21, all of which were within 80.00% ~ 125.00%. There was no significant difference in Tmax between test preparation T and reference preparation R in the results.

Table 2
Bioequivalence analysis of main pharmacokinetic parameters of subjects after single oral administration of test preparation T and reference preparation R.

Parameter	GM(N = 40)			%CV	90% CIs	Power%
	T	R	GMR			
Cmax	876.69	920.89	95.20	19.61	88.48 ~ 102.43	98.89
AUC0-t	986.67	1012.31	97.47	9.52	94.04 ~ 101.02	100.00
AUC0-∞	1008.20	1032.19	97.68	9.44	94.27 ~ 101.21	100.00

Effects of CYP2C19 phenotypes on PKs.

The study recruited 40 volunteers totally, and genotype the three SNPs of CYP2C19. Of the 40 subjects completing the study, 40 subjects were divided into EM (N = 12), IM (N = 24), and PM (N = 4). The AUC C_{max} $T_{1/2}$ CL and V_d of Test and Reference preparation values (μg×hr/L) are shown as mean in Table 3. The pharmacokinetic comparability between Test and Reference was also shown when analyzed separately by CYP2C19 genotype, which were close as well. According to the CYP2C19 phenotype, the plasma concentration time curves of the test preparation and the reference preparation are shown in Fig. 3. The plasma concentration of two preparations increased rapidly after single-dose administration in all 3 groups. The data showed that the blood concentrations of the three groups of volunteers vary greatly with time after oral administration of the drug. After taking the same dose at the same time, because the clearance rate of PM group is the lowest and the half-life time is the longest, the maximum blood concentration and the AUC of the subjects in this group will reach the maximum. On the contrary, the maximum blood concentration and the AUC in EM group were the smallest. However, in terms of absorption, there is no significant difference in the time required for the three groups to reach the maximum concentration of the two drugs in vivo, and the maximum Tmax of the PM group may indicate that the absorption coefficient in this group is relatively small in the three groups. As shown in Fig. 4. In terms of drug distribution, the apparent distribution volume of volunteers in EM group is the largest, but there is no significant difference between IM and PM groups, indicating that drugs are widely distributed in EM group, while drugs are mainly concentrated in blood and less distributed in surrounding tissues in IM and PM. For that, the CYP2C19 phenotypes have little effect on the absorption of drugs in human body, and the main effect lies in drug metabolism.

Table 3
The PK of Reference Preparation and Test preparation in relation to CYP2C19 phenotypes.

CYP2C19 gene polymorphisms	AUC_{0-t}(h*ng/mL)		C_{max}(ng /mL)		$T_{1/2}$(h)		T_{max}	
	T	R	T	R	T	R	T	R
EM(N = 12)	552.90 ± 391.42	591.09 ± 401.03	633.25 ± 295.94	690.50 ± 338.19	0.74 ± 0.19	0.78 ± 0.17	0.29 ± 0.15	0.26 ± 0.10
GMR	0.94		0.92		NA		NA	
IM(N = 24)	1520.14 ± 1437.90	1475.31 ± 1356.51	1044.21 ± 320.07	1060.33 ± 303.17	1.13 ± 0.65	1.11 ± 0.63	0.27 ± 0.08	0.25 ± 0.10
GMR	1.03		0.99		NA		NA	
PM(N = 4)	4526.56 ± 651.59	4913.02 ± 738.77	1650.00 ± 451.66	1670.00 ± 530.28	2.48 ± 0.24	2.46 ± 0.16	0.34 ± 0.12	0.44 ± 0.38
GMR	0.92		0.98		NA		NA	

Discussion

Omeprazole has been widely recognized and used as the first generation of new acid inhibitors once discovered. Different enteric coatings is necessary to protect acid unstable PPI from gastric acid degradation within the stomach, which has the potential detriment of PPI absorption delayed[19]. But omeprazole sodium bicarbonate dry suspension can overcome this problem. Sodium bicarbonate can not only protect omeprazole from being destroyed by gastric acid, but also can quickly neutralize gastric acid, increase the pH value in the stomach, relieve some clinical symptoms, and activate the proton pump channel in a large amount. Omeprazole can directly act on the proton pump channel to inhibit the secretion of gastric acid by the proton pump. The first purpose of this study is to find out the bioequivalence of the reference preparation and the tested preparation. Omeprazole has highly variable pharmacokinetics, of which CYP2C19 is a major influencing factor. Since the relative frequency of CYP2C19 genotypes differs not only between different races, but also in different study populations, it is important to understand the composition of CYP2C19 gene polymorphisms in the study population and the intra-subject variation of different genotypes. And sex may help design future comparative pharmacokinetic studies of omeprazole. CYP2C19 is a polypeptide containing nearly 500 amino acids. It belongs to an important drug metabolizing enzyme in the liver cytochrome P450 enzyme series. It participates in the metabolism of many important drugs in the body. The gene is highly polymorphic, and there are many base mutations in the coding and non-coding regions of the gene. This mutation will further affect enzyme activity, lead to changes in the clearance rate of enzyme substrate drugs, and change the metabolism of drugs in vivo. Affect the efficacy or lead to adverse drug reactions. The reason why the CYP2C19 genotype was studied is because its homozygous, heterozygous and mutant

genotypes have significant differences in the metabolism of drugs in vivo. In this study, a total of 125 subjects were selected, of which 40 subjects were successfully selected into the group, all the subjects completed the test, and no subjects dropped out halfway. The concentration time curves of the two formulations were almost identical (Fig. 1). In addition, both preparations were well tolerated without any serious adverse events. There were no newly reported adverse events in the present study, and there was no significant difference in the frequency of drug-related adverse events between these two formulations. In our study, the AUC of PM group was 8 times higher than that of EM group. Therefore, the increase of AUC, Cmax and T1 / 2 of OME in PM group seems to be due to the decrease of CYP2C19 activity. The results were consistent with previous[22–25] study. There are same differences in PK parameters among different races and groups. Significant differences have been observed between PM and EM groups in several studies conducted in Pakistan, Korea, and Japan. Ethnic differences in CYP2C19 activity can be found in subgroups of the same genotype[26–28]. In this study, the CYP2C19 PM group showed that the AUC inhibition of omeprazole was the largest, which was consistent in previous studies, and in other studies, the degree of gastric acid inhibition was related to omeprazole's AUC[29, 30]. Due to the wide treatment window of omeprazole according to the CYP2C19 phenotype, there seems to be no safety problem with omeprazole[29]. But in our study, because of blood concentration of Group EM was remarkable lower than Group PM, and the incidence of ADR in EM group was lower than that in PM Group, so Group PM was more likely to cause adverse reactions when taking the same administration. In some studies, they compared the PK parameters between single and repeated administration. The AUC values of three groups after repeated administration of omeprazole were higher than those of single dosing[29, 31].They also assessed the intragastric pH by 24-h pH monitoring, Which showed that the AUC0→12hr increased under administration, the clinical efficacy of omeprazole on reducing gastric pH was increased in three groups[28]. For omeprazole metabolism, the main metabolic enzyme is CYP2C19, the secondary metabolic enzyme is CYP3A4. Besides, many studies found the rapid-activity CYP2C19*17 allele was consisted of two sites: -3402C > T and − 806C > T, and the latter one which can increase CYP2C19 transcriptional activity [32]. The Dutch pharmacogenomics working group guidelines recommend that doses should be adjusted according to changes in patient's CYP2C19 metabolism to increase the awareness of adverse drug reactions in all patients [33]. And we eliminated the CYP2C19*17 mutation of the subjects. It has been reported that Omeprazole is metabolized by CYP2C19 much more than CYP3A4[34]. Therefore, the CYP3A4 genotypes of the subjects were not analyzed in this study. In addition, gender may also affect the pharmacokinetic parameters of the drug, thus changing the efficacy of the drug. Shabnam Nazir's study showed that the C_{max}, elimination half-life of omeprazole of females were higher than that of males. Compared with the 95% confidence interval, the C_{max} and C_{max} of 5-hydroxyomeprazole and omeprazole siphon of women were much higher than those of men[35]. The AUC of omeprazole was significantly higher in women, and its elimination time was longer than that in men.

Our limitation of this study is that the pharmacodynamics parameter could not be evaluated. Another possible limitation is that we do not consider the gender of the subjects, which had reported that Cmax and AUC of female ome increased significantly. Besides, we did not assess the PD parameters, which could provide more data to prove the correlation between AUC and pH values.

Conclusion

To sum up, in this study, CYP2C19 * 2 and * 3 was found to affect the PK parameters of omeprazole and sodium bicarbonate in Chinese healthy subjects. Since this study only included healthy people, further research is needed to assess whether there are differences in omeprazole PK / PD profiles among patients with acid-related diseases.

Declarations

Data availability

All data generated or analysed during this study are included in this supplementary information files.

ETHICS STATEMENT

This research was conducted under the guidance of the Declaration of Helsinki, Good Clinical Practice (GCP) guidelines of China Food and Drug Administration (CFDA) and authorized by the independent ethics committee of Tongji Medical College, Huazhong University of Science and Technology (No. (2018)186-1). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

Rui Zhang contributed to the conception of the study, Jinping Zhou; Jiuli Zhou and Chunxiao Yang performed the experiment, Jing Wan contributed significantly to analysis and manuscript preparation, Pengpeng Guo performed the data analyses and wrote the manuscript; Yani Liu and Shaojun Shi funded the successful completion of this experiment.

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Figures

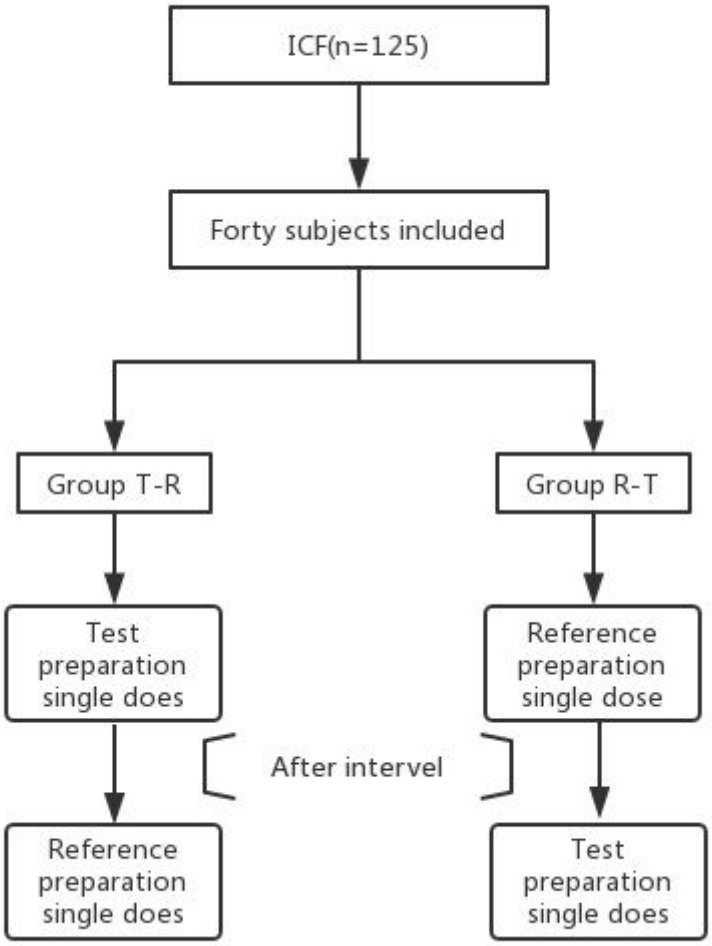

Figure 1

Trial profile.

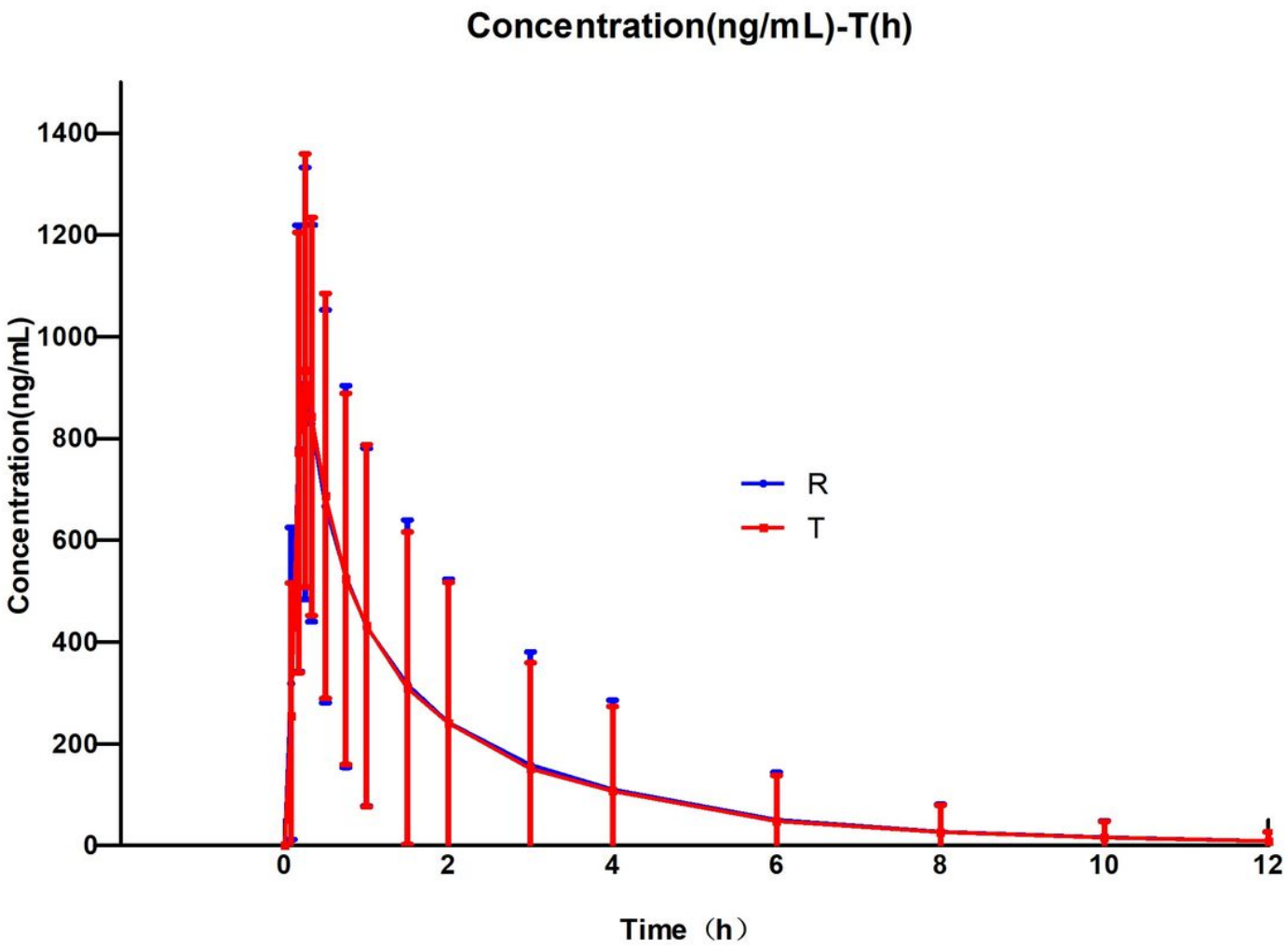

Figure 2

Plasma concentration-time curves of Test preparation and Reference preparation

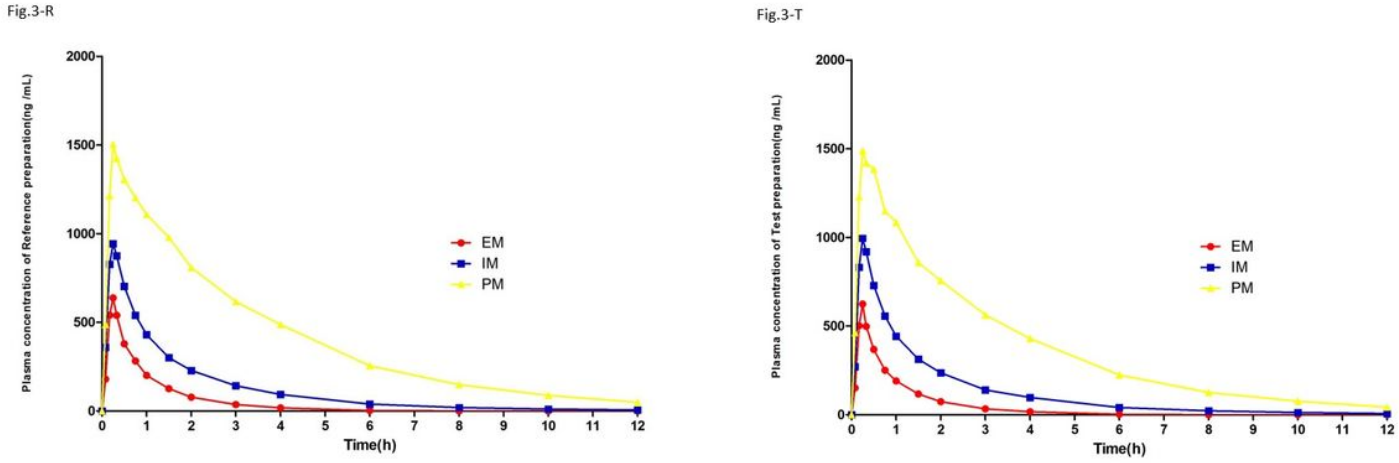

Figure 3

Plasma concentrations of Test and Reference Preparation in relation to CYP2C19 phenotypes. (PK = pharmacokinetic, PM = poor metabolizer, IM = internal medicine, EM = emergency medicine.)

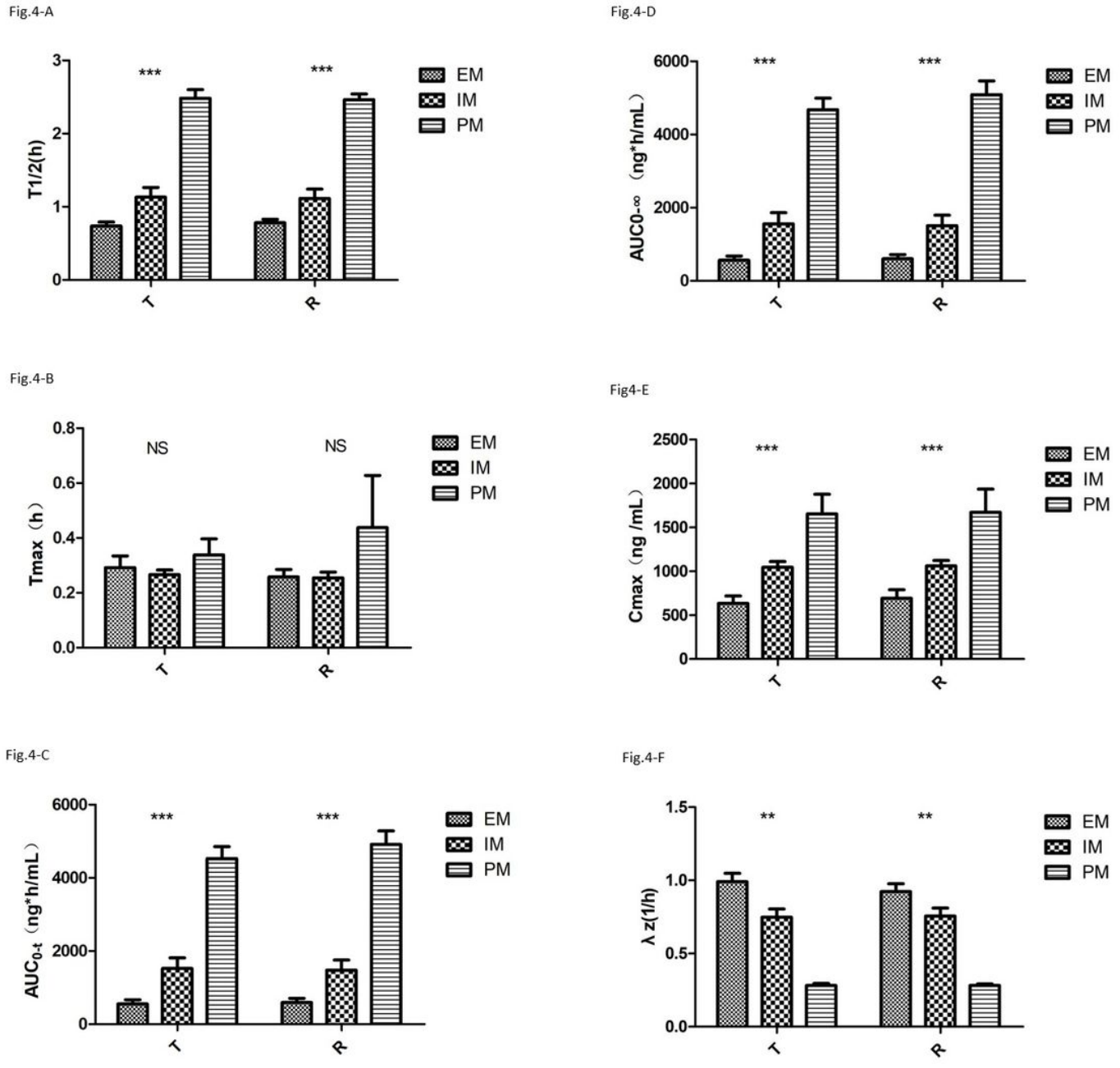

Figure 4

Pharmacokinetic parameters among subjects with different CYP2C19 genotypes after oral administration of test preparation and reference preparation

Supplementary Files

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- rawdata.xlsx