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Pharmacokinetics of the new proton pump inhibitor ilaprazole in Chinese healthy subjects in relation to *CYP3A5* and *CYP2C19* genotypes

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Abstract

Background: PPIs are widely used in peptic diseases, and this paper is to investigate the kinetic characteristics of a new PPI ilaprazole in Chinese healthy subjects and the association with *CYP3A5* and *CYP2C19* polymorphisms.

Methods: 21 subjects were selected and treated with 10mg ilaprazole according to their *CYP3A5*3* genotypes (including 7 of *CYP3A5*1/*1*, 7 of *1/*3*, and 7 of **3/*3*). The plasma concentrations of ilaprazole and its metabolites were monitored by LC-MS/MS method.

Results: The C_{max}, $AUC_{(0–6)}$, $AUC_{(0–48)}$ and $AUC_{(0–\infty)}$ of ilaprazole were all significantly different across the 3 *CYP3A5* genotypes (including 4 of *CYP3A5*1/*1*, 4 of **1/*3*, 3 of **3/*3*; $P<0.05$) in *CYP2C19* wild-type subjects (*CYP2C19* wt/wts), similar variety of C_{max} and $AUC_{(0–6)}$ among *CYP3A5* genotypes (including 3 of *CYP3A5*1/*1*, 3 of **1/*3*, 4 of *3/*3; $P<0.05$) were also observed in *CYP2C19* heterozygous subjects (*CYP2C19* wt/mts). The sulfoxidation metabolic index (measure of collective CYP3A activity) indicates that the *CYP3A5*1/*1* (high-expressers), **1/*3* (low-expressers), and **3/*3* (no-expressers) groups have medium, lowest and highest activities on ilaprazole metabolism, inconsistent with genotype-based CYP3A5 enzymatic activity. Further analysis showed no correlation between ilaprazole metabolism and *CYP2C19* genotypes, evidenced by that the $AUC_{(0–\infty)}$ of ilaprazole from either *CYP3A5*1/*1* or *CYP3A5*1/*3* groups was much higher in *CYP2C19* wt/wts ($n=4$) than that in *CYP2C19* wt/mts ($n=3$) ($P<0.001$), but the C_{max} and $AUC_{(0–6)}$ of ilaprazole from CYP3A5*3/*3 groups, were significantly lower in *CYP2C19* wt/wts ($n=3$) compared to *CYP2C19* wt/mts ($n=4$) ($P<0.01$).

Conclusions: There was no demonstrated relationship between ilaprazole metabolism and *CYP3A5* polymorphisms.

Keywords

Ilaprazole; *CYP3A5*; *CYP2C19*; Pharmacokinetics; Genetic polymorphisms

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1. Introduction

Proton pump inhibitors (PPIs) are highly effective drugs that are widely used in the treatment of peptic diseases including gastric and duodenal ulcer, reflux oesophagitis and Zollinger–Ellison syndrome [1–3]. Many new therapeutic drugs with similar structures and better therapeutic outcomes have been developed since omeprazole first went to marketing, including rabeprazole, pantoprazole, lansoprazole, esomeprazole and the new molecule we studied in this paper, ilaprazole {2-[[(4-methoxy-3-methyl)-2-pyridinyl]methylsulfinyl-5-(1H-pyrrol-1yl)-1H-benzimidazole, CAS 172152-36-2)} (It was also called as IY81149 before, MW 366.4) which was developed by IlYang Pharmacy Co. (Seoul, Korea) and was first studied *in vivo* via experimental animal models of mouse, rats, dogs and pigs [4–6]. These studies found that ilaprazole significantly prevented the development of reflux oesophagitis and gastric secretion in a dose-dependent manner [4], and at the same time had little effect on the animal's cardiovascular system, autonomic nerve system or smooth muscle function from 0.3 to 1000 mg/kg, indicating ilaprazole has a broad dose range and safety feature [5,6]. Up-to-date, there was only one clinical study on patients with gastroesophageal reflux disease, showing that administration of 10 and 20 mg ilaprazole produced a statistically significantly greater and prolonged suppression of gastric pH than 20 mg omeprazole [7].

Today it is clear that most PPIs are largely metabolized by liver cytochrome P450 enzyme CYP2C19 [8–11], but some reports state that CYP3A4 or other enzymes might play more critical roles than CYP2C19 does on lansoprazole and esomeprazole clearance [12–17]. *In vitro* P450 enzyme studies with human liver microsomes in our laboratory found that CYP3A4-selective inhibitors troleandomycin and ketoconazole can significantly increase ilaprazole concentrations and anti-P450 3A4 antibodies have similar effects, while fluvoxamine, a specific CYP2C19 inhibitor showed no effects on ilaprazole metabolism at all (data unpublished). A study with rats using on-line HPLC/ESI mass spectrometry revealed 2 metabolites of ilaprazole, a major product, ilaprazole sulfone, and a minor product, hydroxyilaprazole [18], suggesting that ilaprazole might be dominantly metabolized in the liver by CYP3A and partly by CYP2C19 [34]. In all, *in vitro* and *in vivo* evidence supporting CYP3A and CYP2C19 may display roles on in the systemic elimination of ilaprazole. But as the most important enzyme in CYP3A, CYP3A4 has a large number of different substrates [19,20], and high interindividual variability as large as 20–40 fold has been reported in the population supposedly due to alternative gene splicing or regulators like PXR/CAR [21], these factors are at present difficult to genotype for.

In contrast, *CYP3A5* genotypes are closely associated with CYP3A4 enzyme activity due to their similar substrates, and may contribute to more than 50% of clinically observed interindividual and interracial variability [22–25]. It has been identified two major *CYP3A5* polymorphic alleles (the *CYP3A5*3* and **1*) in the Chinese population [26–30], the genotypes and phenotypes relationships are the homozygous *CYP3A5**1/*1 (high-expressers), heterozygous *CYP3A5**1/*3 (low-expressers), and homozygous *CYP3A5**3/*3 (no-expressers). In addition, the *CYP3A5*3* SNP (6986GNA) in exon 3 is the primary allelic variant in the Chinese population, which has a high allele frequency of 77.8%, and produces a truncated non-functional CYP3A5 protein [26–30]. Therefore, the genetically

polymorphic expression of CYP3A5 may partly explain the interindividual differences of the collective CYP3A activity. In this regard, this study was intended to examine whether single nucleotide polymorphisms (SNPs) of *CYP3A5**3 and *1 alleles affected metabolism of ilaprazole after ingestion of a single dosage of 10 mg ilaprazole in healthy Chinese subjects, and also investigated the possible roles of *CYP2C19**2 and *CYP2C19**3 (2 common SNPs in *CYP2C19*) on ilaprazole metabolism.

2. Materials and methods

2.1. Materials

Ilaprazole (named IY-81149 before, 5 mg enteric-coated tablet), together with research-grade ilaprazole and ilaprazole sulfone standards (colorless crystal powers, purity: 99.1%) were provided by Livzon Pharmaceutical Group Inc. (Zhuhai, China), which signed a license agreement and got the patent from ILYANG Pharmaceutical Company Ltd. (Seoul, South Korea). The chemical structure of ilaprazole and ilaprazole sulfone are shown in Fig. 1. Omeprazole, the internal standard, was from Sigma Chemical Co. (purity: 99.5%, St. Louis, MO). HPLC-grade acetonitrile, methanol and formic acid were from Dikma Comp (Guangzhou, China). HPLC-grade water was from a Milli-Q system (Millipore, Milford, MA). All other reagents were of analytical grade.

2.2. Subjects

202 healthy Chinese volunteers were screened for *CYP3A5**3 genotypes and 21 adult men were selected to participate in this study based on their *CYP3A5**3 genotypes, after which they were genotyped for *CYP2C19**2 and *CYP2C19**3 (Table 1). The study was approved by the Ethics Committee Board of Xiangya School of Medicine, Central South University, Hunan, China. All the subjects provided written informed consent.

All were students at Xiangya School of Medicine, Central South University and were nonsmokers with no history of significant medical illness. Demographic and clinical characteristics of subjects enrolled in the study are shown in Table 1. Physical examination, blood chemistries screen (including a complete blood count, liver function test), urinalysis and electrocardiogram performed before the study. Not including those receiving PPIs or other drugs within the last month; alcohol consume within 2 weeks or hypersensitivity to drugs. All volunteers were served standard meals at 12:00PM and 18:00PM and closely monitored in case of any adverse effects that may occur during the experiment. The use of alcohol, tea, coffee, cola and fruit juice was forbidden during the test days.

2.3. Study design and clinical protocol

The order of administration was randomized according to a random-number table. All the volunteers received a single oral dose of ilaprazole (5 mg tablet, 2 pills) with 250 ml of warm water after an overnight fast. Ilaprazole was given at 8 AM, and blood samples (5 ml each) were drown into heparinized tubes from the antecubital vein immediately before (0 min) and at 1, 2, 3, 4, 5, 6, 8, 10, 12, 24 and 48 h after dosing, meals is served 4 h after drug is been taken. Within 15 min blood samples were centrifuged at 2500×*g* for 10 min,

and plasma was separated and maintained at −80 °C until the determination of ilaprazole and its metabolite ilaprazole sulfone.

2.4. CYP3A5 and CYP2C19 genotyping

Genomic deoxyribonucleic acid (DNA) was extracted from peripheral lymphocytes with phenol–chloroform followed by ethanol precipitation. All genotyping analysis was conducted by the polymerase chain reaction — restriction fragment length polymorphism (PCR-RFLP) assay. The PCR of *CYP3A5* gene was performed using the primer pair as follows: the sense primer P1 (5′-catgacttagtagacagatgac-3′) and the antisense primer P2 (5′-ggtccaaa-cagggaagaaata-3′). The final 25 μl of PCR mixture contained 12.6 μl of PCR-grade water, 2.5 μl of 10×PCR buffer, 2.0 μl of deoxyribonucleoside triphosphates (dNTP, 2.5 μmol/l each), 0.8 μl of primer (10 μmol/l each), 0.3 μL of r*Taq* DNA polymerase (5 U/μL, TaKaRa Biotech, Dalian, China), and 1.0 μL of genomic DNA sample. Temperature cycling proceeded as follows: initial denaturation for 5 min at 94 °C, followed by 35 cycles of 30 s at 94 °C, 30 s at 60 °C, 30 s at 72 °C, and a terminal extension for 7 min at 72 °C. The amplified DNA fragments including the homozygous **1*, heterozygous **1*/**3*, and homozygous *3 alleles were digested with *Ssp*I (TaKaRa Biotech) at 37 °C for 4h. The different patterns of the digested fragments were visualized on ethidium bromide-stained 4% agarose gel.

Genotyping identifying *CYP2C19* wild-type gene and its 2 mutated alleles, *CYP2C19***2* in exon 5 and *CYP2C19***3* in exon 4 were performed as originally described [31,32] with minor modifications. The *CYP2C19***2* (G681A) polymorphic locus was amplified by the use of the sense primer P3 (5′-cagagcttggcatattgtatc-3′) and the antisense primer P4 (5′-gtaaacacacaactagtcaatg-3′). The reaction system and amplification conditions were similar to those of the *CYP3A5***3*, except that the denaturation temperature was 47 °C. The amplified DNA fragments including mutation site were digested with *SmaI* (TaKaRa Biotech) at 30 °C for 8 h and the digested fragments were judged on ethidium bromide-stained 3% agarose gel.

Because the human *CYP2C19***3* (G636A) locus was GC-rich, a commercial advantage GC-rich genomic PCR buffer (TaKaRa Biotech) was used to obtain better amplication, and we used the primer pair as follows: the sense primer P5 (5′-aaattgtttccaatcatttagct-3′) and the antisense primer P6 (5′-acttcagggcttggtcaata-3′). The final 25 μl of PCR mixture contained 3.5 μl of PCR-grade water, 12.5 μl of 2×GC PCR buffer, 2.0 μl of dNTP (2.5 μmol/l each), 4.0 μl of $MgCl_2$, 0.4 μl of primer (10 μmol/l each), 0.2 μl of LA*Taq* DNA polymerase (5 U/μl), and 2.0 μl of genomic DNA sample. Temperature cycling proceeded as follows: initial denaturation for 1 min at 94 °C, followed by 35 cycles of 20 s at 94 °C, 20 s at 53 °C, 30 s at 72 °C, and a terminal extension for 7 min at 72 °C. The PCR products were digested by *BamH*I (TaKaRa Biotech) at 37 °C for 8 h and then visualized on ethidium bromide-stained 4% agarose gel.

2.5. Plasma ilaprazole and its metabolite concentration measured by LC-MS/MS

Plasma concentrations of ilaprazole and ilaprazole sulfone were determined by a new liquid chromatography-tandem mass spectrometric (LC-MS/MS) method developed in our

laboratory. To date, the assumed hydroxylated metabolite (possibly by CYP2C19) of ilaprazole in human is not available; so the hydroxylated metabolite (the hydroxy) has not been quantified in this study.

A mixture of 500 μl human plasma and 100 μl the internal standard solution (594 ng/ml omeprazole) were extracted with 5 ml of trichlormethane by vigorously shaking for 2 min, and then centrifuged at 2500 rpm for 10 min. An aliquot of 4 ml of the organic extract was then decanted and evaporated to dryness under liquid nitrogen. The residue was reconstituted with 100 μl mobile phase and 10 μl of this solution was injected into the LC-MS/MS system. An XTerra MS C18 packed column (50×2.1mm; particlesize, 5 μm; Waters Corporation) was used as an analytic column. The mobile phase was a mixture of 0.025mol/l potassium dihydrogen phosphate: acetonitrile (60:40, v/v) and pumped at a flow rate of 0.2 ml/min. The retention times were 1.2, 1.28 and 1.65 min for ilaprazole, ilaprazole sulfone and omeprazole (internal standard). The inter-day precision and accuracy and the coefficient of variance (CV) were all <15%, demonstrating good reproducibility. The limit of quantitation for ilaprazole and ilaprazole sulfone was 0.36 ng/ml and 0.25 ng/ml, respectively. The LC system was a ThermoFinnigan Surveyor liquid chromatography equipped with an isocratic pump, an autosampler and a degasser. Mass spectrometric analysis was performed usinga LCQ Deca XP instrument from Finnigan with an ESI interface. The data acquisition and control system were created using Xcalibur 1.3 software from Finnigan.

2.6. Pharmacokinetic analyses

All of the pharmacokinetic parameters were calculated by use of WinNonlin (Pharsight Corporation, ver. 3.0, Mountain View, CA). The elimination rate constant (λ) was determined by the least square fitted terminal log-linear portion of the plasma concentration–time profile, and the elimination half-life ($t_{1/2}$) was calculated as 0.693 divided by λ. The area under the plasma concentration–time curves (AUCs) of ilaprazole and its metabolite were calculated by the linear trapezoidal rule and further extrapolated to infinity by dividing the last measurable concentration by λ as $AUC_{(0-t)}+C_{last}/\lambda$. The apparent oral clearance (Cloral) of ilaprazole was calculated as Cloral=Dose/$AUC_{(0-\infty)}$. The maximum plasma concentration (C_{max}) and the corresponding peak times (t_{max}) were determined by visual inspection of plasma concentration–time data. The sulfoxidation metabolic index was calculated as $AUC_{(0-\infty)}$ of ilaprazole sulfone/$AUC_{(0-\infty)}$ of ilaprazole.

2.7. Statistics analyses

Data were compiled according to the genotypes and summarized as Means± SD together with the 95% confidence intervals in the text. The pharmacokinetic parameters of ilaprazole and its major metabolite ilaprazole sulfone across the 3 *CYP3A5*3* groups were compared using one-way ANOVA followed by Scheffe's test, and statistical significance between each 2 groups were tested via independent-samples *t*-test or the Wilcoxon signed-rank test when there is no variance homogeneity. A $P<0.05$ was considered as statistically significant. All statistical analyses were performed with the statistical program SPSS 13.0 for Windows (SPSS Inc., Chicago, IL).

3. Results

3.1. Genotyping for CYP3A5 and CYP2C1

No subject in this study was found to be homozygous for the *CYP2C19*2* or *CYP2C19*3* mutations. The allele frequencies of the *CYP2C19*2* and *CYP2C19*3* mutations in our subjects were 0.36 and 0.07 (data not shown), respectively. *CYP3A5*3* frequencies occurred at 75.3% of the population in the present study, consistent with the data previously reported in the Chinese Han population [30].

3.2. Pharmacokinetics of ilaprazole

As a whole, the mean area under the plasma concentration–time curve calculated from time zero to infinity ($AUC_{(0-\infty)}$) in the *CYP2C19* wt/wts group was significantly higher compared to that in the *CYP2C19* wt/mts group (1734.1±1160.0ng h l^{-1} vs 861.0±240.8ng h l, P=0.031) (Fig. 2). The $AUC_{(0-\infty)}$ of ilaprazole sulfone showed an incredible increase in *CYP2C19* wt/mts compared to *CYP2C19* wt/wts (2167.4±1255.5ng h l^{-1} vs 1065.7±694.6ng h l^{-1}, P=0.020) (Fig. 2).

The pharmacokinetic parameters of ilaprazole and ilaprazole sulfone in each group are shown in Figs. 3 and 4 and Tables 2 and 3. The peak plasma concentration (C_{max}), $AUC_{(0-6)}$, $AUC_{(0-48)}$ and $AUC_{(0-\infty)}$ of ilaprazole was lowest in the *CYP3A5*3/*3* (non-expressers, n = 3) group, medium in the *CYP3A5*1/*1* (high-expressers, n = 4) group and highest in *CYP3A5*1/*3* (low-expressers, n = 4) groups within *CYP2C19* wt/wts subjects (Table 2), in line with the oral elimination of ilaprazole (CL/F) across the three groups. The fact that the AUC in *CYP3A5**1/*1, *1/*3 and *3/*3 is medium, highest and lowest, respectively, is suggesting a lack of effect of CYP3A5 on ilaprazole metabolism (especially since the lowest AUC is observed in CYP3A5 non-expressers, i.e. *CYP3A5**3/*3). Within *CYP2C19* wt/mts subjects, the $AUC_{(0-6)}$ of ilaprazole was significantly lower in *CYP3A5*3/*3*s (n = 4) with respect to *CYP3A5*1/*1*s (n = 3) or *CYP3A5*1/*3*s (n = 3), and C_{max} was significantly lower in *CYP3A5*3/*3*s compared to *CYP3A5*1/*3*s (Table 2). Again, there is no trend in AUC and C_{max} from *CYP3A5**1/*1, *1/*3 to *3/*3 genotypes, inconsistent with regard to the expected CYP3A5 phenotypes. Other parameters showed no significant differences. Consistent with AUC data, sulfoxidation metabolic index values of ilaprazole sulfone were also observed medium, lowest and highest in *CYP3A5*1/*1*, **1/*3* and **3/*3* within both *CYP2C19* wt/wts and wt/mts subjects (Table 3), further supporting no correlation between *CYP3A5* genotypes and ilaprazole metabolism. No obvious differences in T_{max} or $t_{1/2}$ values of ilaprazole and ilaprazole sulfone were found across the three *CYP3A5*3* groups.

Moreover, the C_{max}, AUC of ilaprazole in *CYP2C19* wt/mts subjects was significantly lower than that of *CYP2C19* wt/wts subjects within the *CYP3A5*1/*3* (Table 2, P<0.001), which exhibited a reverse trend against the classic CYP2C19-mediated metabolism. Similarly, the same index values were all approximately two times greater in *CYP2C19* wt/wts subjects compared with *CYP2C19* wt/mts subjects within the *CYP3A5*1/*1*, but this difference did not reach statistic significance possibly because of small sample sizes. However, the C_{max} and $AUC_{(0-6)}$ of *CYP2C19* wt/wts subjects was much lower compared to that of

CYP2C19 wt/mts subjects within the *CYP3A5*3/*3* (Table 2, $P<0.01$), but the $AUC_{(0–48)}$ and $AUC_{(0–\infty)}$ of ilaprazole sulfone of *CYP2C19* wt/wts was also significantly lower than that in CYP2C19 wt/mts within *CYP3A5*3/*3* (Table 3, $P<0.05$).

As reported that the sulfoxidation metabolic index is correlated with the level of CYP3A enzymes in human liver microsomes [15]. In this paper the $AUC_{(0–\infty)}$ ratio of ilaprazole sulfone to ilaprazole was calculated to evaluate the sulfoxidation ability that equals to the collective CYP3A activity. The relative sulfoxidation metabolic index ratios were 2.6:1:9.6 in *CYP3A5*1/*1*, **1/*3* and **3/*3* (Table 3, Fig. 5). No clinically undesirable effects were observed throughout the study period. All volunteers completed the study according to the protocol.

4. Discussion

This was the first time to investigate the relative contributions of *CYP3A5* genetic polymorphisms to the new PPI drug ilaprazole in healthy Chinese subjects by measuring the kinetic parameters of ilaprazole and its major metabolite ilaprazole sulfone [18], also try to investigate whether *CYP2C19* polymorphisms are involved in ilaprazole metabolism.

Our results revealed that the main parameters of ilaprazole and its major metabolite ilaprazole sulfone were all significantly changed across the three *CYP3A5* genotypes within *CYP2C19* wt/wts or wt/mts subjects. Although CYP3A5 high-expressers (*CYP3A5*1/*1*s) showed higher clearance than CYP3A5 low-expressers (*CYP3A5*1/*3*s). Unexpectedly, CYP3A5 no-expressers (*CYP3A5*3/*3*s) displayed the highest drug clearance among the three *CYP3A5* genotypes. In this regard, *CYP3A5*1/*1*, *CYP3A5*1/*3* and *CYP3A5*3/*3* had the moderate, the lowest and the highest ability to metabolize ilaprazole, respectively (Table 2). These results indicate that the lacking CYP3A5 enzyme activity has nothing to do with the ilaprazole metabolism. Given *CYP3A5* genotype–phenotype were not in line with the collective CYP3A enzyme activity among three groups as we expected, we can't use *CYP3A5* genotypes to represent the collective CYP3A enzyme activity in this particular study, and some unknown candidate enzyme or other metabolizing pathways may exist for these discrepant results.

As no demonstrated gene–dose effect was found to be associated with *CYP3A5*3* genotypes, we subsequently group the whole subjects on *CYP2C19* genotypes and try to investigate whether *CYP2C19* polymorphisms play a role in ilaprazole metabolism. The results showed that the $AUC_{(0–\infty)}$ of ilaprazole was significantly higher in *CYP2C19* wt/wts than that in *CYP2C19* wt/mts. This was in accordance with a markedly increase on $AUC_{(0–\infty)}$ of ilaprazole sulfone in *CYP2C19* wt/mts than that in *CYP2C19* wt/wts (Fig. 2), indicating the opposite of a CYP2C19-mediated metabolism. Next we compared the pharmacokinetic parameters between *CYP2C19* wt/wts and *CYP2C19* wt/mts of each *CYP3A5*3* genotype, which revealed that *CYP2C19* wt/wts had a higher C_{max} and $AUC_{(0–\infty)}$ than *CYP2C19* wt/mts in both *CYP3A5*1/*1*s and *CYP3A5*1/*3*s, but in the case of *CYP3A5*3/*3*s, C_{max} and $AUC_{(0–6)}$ of *CYP2C19* wt/wts was significantly lower than *CYP2C19* wt/mts, indicating no correlation between ilaprazole metabolism and CYP2C19 genotypes.

On the basis of the results, no genotype (*CYP3A5* or *CYP2C19*) is affecting ilaprazole pharmacokinetics; additionally, *in vitro* human liver microsomal studies demonstrating that CYP3A4-selective inhibitors (troleandomycin and ketoconazole) and anti-CYP3A4 antibody can significantly increase ilaprazole concentrations (data unpublished), we speculate that it might be CYP3A4 playing a more crucial role than *CYP3A5* or *CYP2C19* genetic polymorphisms in ilaprazole metabolism. It might also be that the genetic variation of CYP3A4 activity (as large as 20–40 fold) [21] covers the potential individual variation among the *CYP3A5* and *CYP2C19* genotype groups and contributes to *CYP3A5* and *CYP2C19* genotype-independent pharmacokinetics. Previous study in rat found that the CYP3A4 inhibitor quercetin could significantly enhance the beneficial effect of ilaprazole on reflux oesophagitis treatment [4,33], indicating that CYP3A4 might play a role in ilaprazole metabolism. What's more, since the sulfoxidation metabolic index is generally correlated with the collective CYP3A activities in human liver microsomes [15], the relative sulfoxidation metabolic index ratios were calculated as 2.6:1:9.6 in *CYP3A5*1/*1*, **1/*3* and **3/*3* in our study, which might reflect the potential levels of collective CYP3A activities.

To date, there is no solid evidence linking ilaprazole pharmacokinetic characteristics in relation to *CYP3A5* or *CYP2C19* genotypes. As it is well known that most PPIs are metabolized by CYP2C19 [8–11] and these are greatly different between Caucasian and Asian people [35,36], so a study of large samples in European and American populations including *CYP2C19* PMs (mt/mts) that receive repeated dosing ilaprazole would be needed to confirm CYP3A/2C19's function on ilaprazole metabolism.

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Abbreviations:

***CYP2C19* wt/wts**	*CYP2C19* wild-type alleles subjects
***CYP2C19* wt/mts**	*CYP2C19* mutated alleles subjects for *CYP2C19*2* and *CYP2C19*3*
PPIs	proton pump inhibitors
SNPs	single nucleotide polymorphisms

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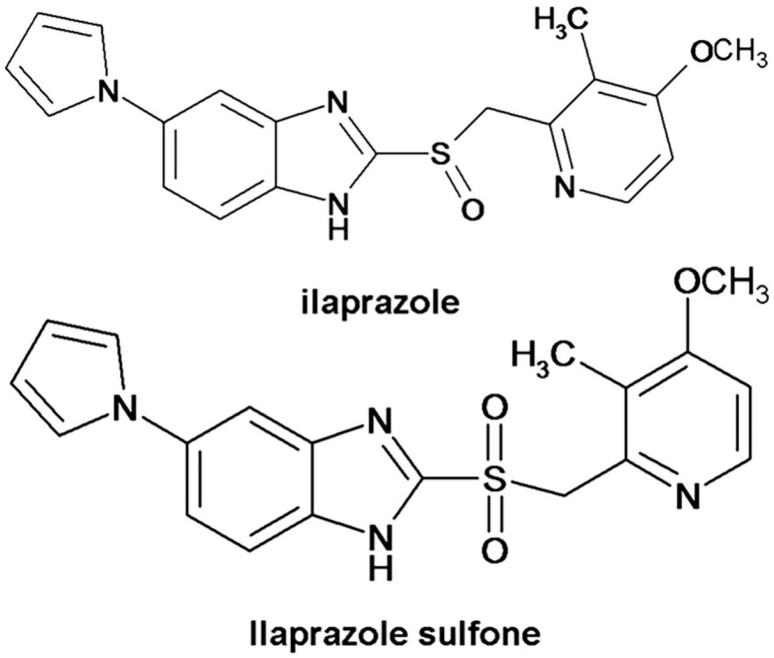

Fig. 1.
Chemical structure of ilaprazole and ilaprazole sulfone.

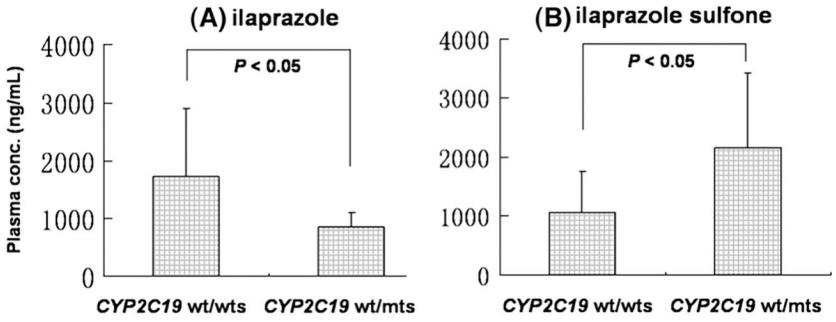

Fig. 2.

Effects of *CYP2C19* genotypes on the $AUC_{(0-\infty)}$ of ilaprazole (A), and ilaprazole sulfone (B) after a single 10 mg oral dose ilaprazole. Error bars indicate SD (CYP2C19 wt/wts (n = 11): wild-type for CYP2C19*2 and CYP2C19*3 mutated alleles subjects; CYP2C19 wt/mts (n = 10): heterozygous for CYP2C19*2 and CYP2C19*3 mutated alleles subjects).

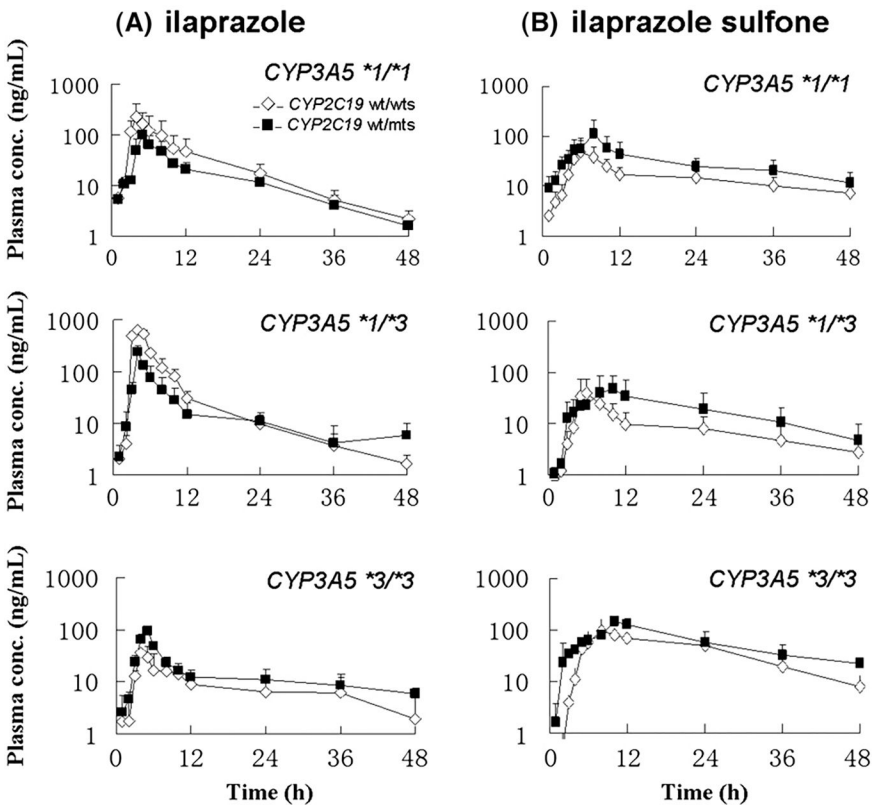

Fig. 3.

Plasma concentration–time curves (mean±SD) of ilaprazole (A), and ilaprazole sulfone (B) after a single 10 mg oral dose ilaprazole between *CYP2C19* wt/wts (open diamonds) and *CYP2C19* wt/mts (close squares) within *CYP3A5*1/*1*s ($n = 7$), *CYP3A5*1/*3*s ($n = 7$) and *CYP3A5*3/*3*s ($n = 7$), respectively.

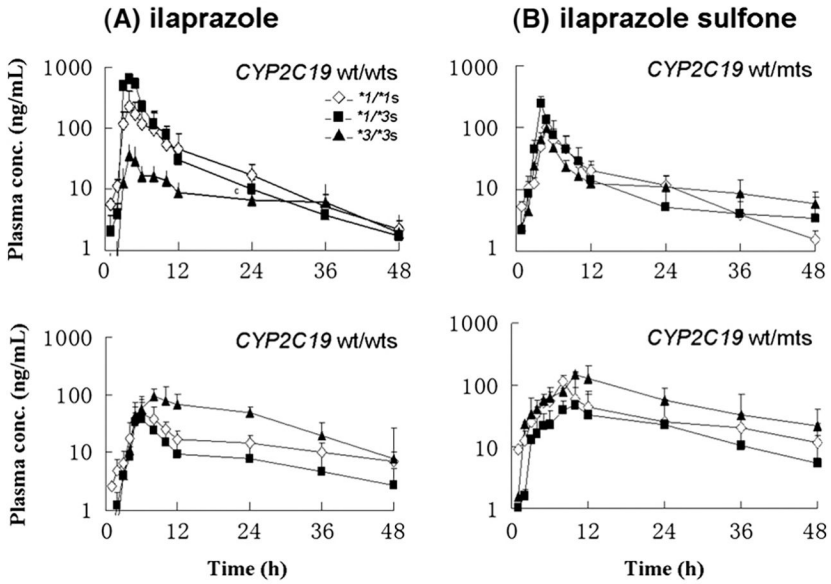

Fig. 4.

Plasma concentration–time curves (mean±SD) of ilaprazole (A), and ilaprazole sulfone (B) after a single 10 mg oral dose ilaprazole among *CYP3A5*1/*1*s (open diamonds), *CYP3A5*1/*3*s (close squares), and *CYP3A5*3/*3*s (close triangles) within *CYP2C19* wt/wts (n = 11) and *CYP2C19* wt/mts (n=10), respectively.

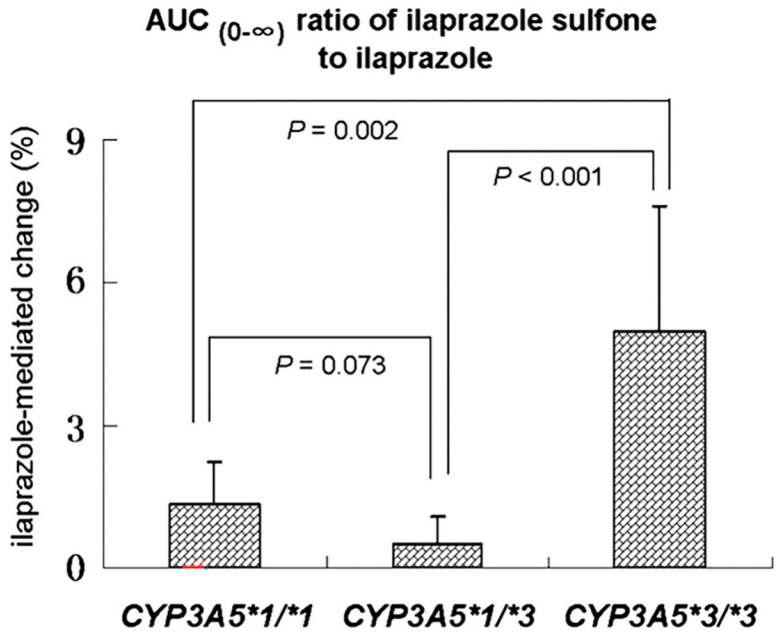

Fig. 5.

Effects of *CYP3A5* genotypes on the mean ilaprazole-mediated increase on sulfoxidation metabolic index (ilaprazole sulfone $AUC_{(0–\infty)}$/ilaprazole $AUC_{(0–\infty)}$). Error bars indicate SD ($n = 21$).

Table 1

Demographic characteristics of the healthy Chinese subjects enrolled in study (n = 21)

Genotype	*CYP2C19* genotype (wt/wts: wt/mts)	Age* (years)	Height* (cm)	Body weight* (kg)
*CYP3A5*1/*1*	4: 3 (n = 7)	22.2±1.8 (20–26)	170.2±6.4 (157–179)	61.2±4.8 (52–76)
*CYP3A5*1/*3*	4: 3 (n = 7)	22.4±1.0 (20–26)	172.0±8.5 (155–181)	60.4±9.0 (44–74)
*CYP3A5*3/*3*	3: 4 (n = 7)	21.7±1.2 (20–25)	170.5±4.5 (162–180)	62.7±11.2 (47–80)

*Values are given as mean±SD (values in parentheses represent the 95% confidence interval); wt/wts, *CYP2C19* wild-type; wt/mts, *CYP2C19*1/*2* or **1/*3*.

Table 2

Ilaprazole pharmacokinetic parameters across the three *CYP3A5* genotypes and two *CYP2C19* genotype groups after an oral dose of 10 mg ilaprazole (PO) in a healthy Chinese population (n = 21)

Ilaprazole	***CYP3A5*1/*1* (*n* = 7)**	***CYP3A5*1/*3* (*n* = 7)**	***CYP3A5*3/*3* (*n* = 7)**
CYP2C19 wt/wts (n = 11)			
C_{max} (ng l^{-1})	241.9±171.3** (30.8, 514.5)	626.8±72.1 (511.9, 741.7)	36.0±18.7$^{***,\#}$ (10.4, 82.3)
T_{max} (h)	4.5±0.6 (4, 5)	4.3±0.5 (4, 5)	4.0±0.0 (4, 4)
$t_{1/2}$ (h)	7.5±1.6 (5.0, 9.0)	5.4±0.5 (4.6, 6.2)	7.8±1.2 (5.2, 9.8)
$AUC_{(0–6)}$ (ng h l^{-1})	587.8±381.8*** (−19.7, 1195.4)	1782.0±229.1 (1417.4, 2146.5)	88.0±33.1$^{***,\#}$ (5.2, 170.5)
$AUC_{(0–48)}$ (ng h l^{-1})	1613.8±1103.2 (−141.7, 3369.2)	2789.3±115.5 (2614.1, 2991.3)	389.2±210.0$^{*,\#}$ (−135.0, 916.7)
$AUC_{(0–\infty)}$ (ng h l^{-1})	1637.6±1100.3 (−113.3, 3388.5)	2803.5±119.6 (2677.5, 2956.3)	432.8±260.2$^{*,\#}$ (−210.7, 1084.5)
CL/F(l h^{-1})	7.9±3.84 (1.9, 14.0)	3.6±0.1 (3.3, 3.8)	31.8±11.9$^{*,\#}$ (12.3, 62.5)
CYP2C19 wt/mts (n = 10)			
C_{max} (ng l^{-1})	101.2±32.5 (20.4, 182.0)	242.0±74.3^{aaa} (57.3, 426.8)	95.2±18.0^{†,bb} (62.3, 113.0)
T_{max} (h)	4.0±0.0 (4, 4)	5.0±0.0 (5, 5)	5.0±0.0 (5, 5)
$t_{1/2}$ (h)	7.9±0.7 (6.4, 9.4)	7.4±2.6 (0.9, 13.8)	9.6±0.8 (8.8, 14.5)
$AUC_{(0–6)}$ (ng h l^{-1})	210.6±76.3†† (21.0, 400.2)	467.2±85.2^{aaa} (255.5, 678.9)	212.1±20.0^{††,bb} (182.3, 244.1)
$AUC_{(0—48)}$ (ng h^{-1})	760.1±130.3 (436.3, 1083.9)	923.7±278.3^{aaa} (232.5, 1614.9)	701.9±182.0 (401.9, 984.8)
$AUC_{(0–\infty)}$ (ng h l^{-1})	777.6±124.2 (468.7, 1086.5)	970.3±340.2^{aaa} (125.2, 1815.5)	839.4±241.8 (420.2, 1261.9)
CL/F(l h^{-1})	13.1±2.3 (7.4, 18.8)	11.2±3.9 (1.5, 20.9)	13.1±5.0 (5.0, 21.0)

Data are shown as mean±SD and 95% confidence interval.

C_{max}, peak plasma concentration; T_{max}, time to peak concentration; $t_{1/2}$, terminal elimination half-life; $AUC_{(0–6)}$, area under plasma concentration–time curve from zero to 6 h; $AUC_{(0–48)}$, area under plasma concentration–time curve from 0 to 48 h; $AUC_{(0–\infty)}$, area under plasma concentration–time curve extrapolated to infinity; CL/F, the oral elimination of ilaprazole time.

$^{*}P<0.05$

$^{**}P<0.01$

$^{***}P<0.001$ compared with *CYP3A5*1/*3*s within CYP2C19 wt/wts subjects.

$^{\#}p<0.05$

$^{\#\#}p<0.01$ compared with *CYP3A5*1/*1*s within CYP2C19 wt/wts subjects.

$^{\dagger}p<0.05$

$^{\dagger\dagger}p<0.01$ compared with *CYP3A5*1/*3*s within *CYP2C19* wt/mts subjects.

$^{\ddagger}p<0.05$

$^{\ddagger\ddagger}p<0.01$ compared with *CYP3A5*1/*1*s within *CYP2C19* wt/mts subjects.

$^{a}p<0.05$

$^{aa}p<0.01$

$^{aaa}p<0.001$ compared with *CYP2C19* wt/wts within *CYP3A5*1/*3*s.

$^{b}p<0.05$

$^{bb}p<0.01$ compared with *CYP2C19* wt/wts within *CYP3A5*1/*1*s.

Table 3

Ilaprazole sulfone pharmacokinetic parameters across the 3 *CYP3A5* genotypes and 2 *CYP2C19* genotype groups after an oral dose of 10 mg ilaprazole (PO) in a healthy Chinese population (n = 21)

Ilaprazole sulfone	***CYP3A5*1/*1 (n = 7)***	***CYP3A5*1/*3 (n = 7)***	***CYP3A5*3/*3 (n = 7)***
CYP2C19 wt/wts (n = 11)			
C_{max} (ng^{-1})	56.5±44.4 (14.2, 127.3)	41.1±35.6 (15.5, 97.9)	106.5±42.8 (0.2, 212.9)
T_{max} (h)	6.8±1.5 (5.0, 8.0)	7.3±3.2 (5.0, 12.0)	9.3±2.3 (8.0, 12.0)
$t_{1/2}$ (h)	21.8±12.4(2.0, 41.5)	12.1±3.8 (6.1, 18.2)	10.9±4.1 (0.6, 21.1)
$AUC_{(0-6)}$ (ng h l^{-1})	89.6±72.7 (−26.0, 205.2)	66.8±64.7 (−36.1, 169.7)	87.5±46.0 (−27.0, 201.9)
$AUC_{(0-48)}$ (ng h l^{-1})	722.7±252.8 (320.4, 1125.0)	419.5±309.8 (−73.5, 912.6)	1839.5±32.9 $^{***,\#\#}$ (1757.7, 1921.3)
$AUC_{(0-\infty)}$ (ng h l^{-1})	975.0±400.6 (337.5, 1612.6)	472.1±352.6 (−88.9, 1033.1)	1978.0±123.7 $^{***,\#\#}$ (1670.7, 2285.3)
Sulfoxidation metabolic index	0.7±0.5 * (0, 1.5)	0.2±0.1 (0, 0.4)	6.0±3.9 $^{*,\#}$ (-3.5, 15.4)
CYP2C19 wt/mts (n = 10)			
C_{max} (ng^{-1})	142.3±82.5 (−62.7, 347.3)	58.1±30.6 (−17.8, 134.0)	171.0±65.1 (67.3, 274.6)
T_{max} (h)	7.7±2.5 (5.0, 10.0)	7.3±3.0 (4.0, 10.0)	11.0±1.2 (10.0, 12.0)
$t_{1/2}$ (h)	13.5±3.2(5.5, 21.5)	12.3±2.7 (5.7, 18.9)	14.3±5.3 (5.9, 22.6)
$AUC_{(0-6)}$ (ng h l^{-1})	162.8±77.7 (−30.3, 355.9)	65.8±30.7 (−10.4, 141.9)	188.1±60.9 † (91.2, 285.1)
$AUC_{(0-48)}$ (ng h l^{-1})	1487.8±472.8 ^{b} (313.2, 2662.5)	986.4±825.5 (−1064.5, 3037.3)	2819.0±651.2 ^{††,‡,c} (1782.8, 3855.3)
$AUC_{(0-\infty)}$ (ng h l^{-1})	1736.6±644.0 (136.9, 3336.4)	1087.5±921.1 (−1200.6, 3375.5)	3300.4±2167.4 ^{†,‡,c} (1856.7, 4744.2)
Sulfoxidation metabolic index	2.1±0.5 (0.9, 3.5)	1.0±0.5 (−0.3, 2.3)	4.2±1.6 ††,‡ (1.7, 6.8)

Data are shown as mean±SD and 95% confidence interval. The sulfoxidation metabolic index was calculated as $AUC_{(0-\infty)}$ of ilaprazole sulfone/$AUC_{(0-\infty)}$ of ilaprazole.

$^{*}P<0.05$

$^{**}P<0.01$

$^{***}P<0.001$ compared with *CYP3A5*1/*3*s within *CYP2C19* wt/wts subjects.

$^{\#}P<0.05$

$^{\#\#}P<0.01$ compared with *CYP3A5*1/*1*s within *CYP2C19* wt/wts subjects.

† $p<0.05$

†† $p<0.01$ compared with *CYP3A5*1/*3*s within *CYP2C19* wt/mts subjects.

‡ $p<0.05$

‡‡ $p<0.01$ compared with *CYP3A5*1/*1*s within *CYP2C19* wt/mts subjects.

b $p<0.05$ compared with *CYP2C19* wt/wts within *CYP3A5*1/*1*s.

c $p<0.05$ compared with *CYP2C19* wt/wts within *CYP3A5*3/*3*s.