Influence of Cytochrome P450 2C19 on the pharmacokinetics of lansoprazole administered by single and successive intravenous infusion in healthy Chinese volunteers

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Abstract

This study aimed to explore the effect of CYP2C19 polymorphisms on the pharmacokinetics of lansoprazole administered by single and successive intravenous (iv) infusions in healthy Chinese volunteers. A total of 30 subjects, including 20 extensive metabolizers (EMs) and 10 poor metabolizers (PMs) were recruited and randomly assigned to three groups receiving doses of 15, 30 and 60 mg. All subjects received a single dose of lansoprazole during a 60-min period, and only the 30 mg dose group continued to receive the same dose iv for the next seven days (twice daily). Plasma concentrations of lansoprazole were monitored by high performance liquid chromatography (HPLC) at the following times: 15, 30, 45, 60, 75, 105, 165, 225, 300, 390, 480, 600 and 720 min after lansoprazole administration. After a single intravenous infusion in the three groups, AUC, C_{max} and $t_{½}$ were significantly higher in PMs than in EMs, while total clearance (Cl_{total}) in PMs was significantly lower than that in EMs. Mean AUC and C_{max} ratios in EMs and PMs were 2.1:1 and 1.4:1, respectively. After repeated doses of 30 mg, the AUC, C_{max}, and $t_{½}$ increased significantly, while the Cl_{total} decreased significantly in EMs. Mean AUC and C_{max} ratios in EMs and PMs amounted to 2.2:1.4 and 1.5:1.2, respectively. Lansoprazole displays a linear increase in AUC and C_{max} over a dose range of 15-60 mg, and these were dependent on individual CYP2C19 status.

Introduction

Numerous studies over the last decade have shown that the proton-pump inhibitors (PPIs) are more effective at reducing gastric acid and sustaining inhibition when compared with the histamine-2 receptor antagonists (H2RA). PPIs currently available on the market include omeprazole(OPZ), lansoprazole (LPZ), pantoprazole (PPZ), rabeprazole (RPZ), esomeprazole (EPZ) and ilaprazole (IPZ).[1,2] By targeting the membrane H^+/K^+-adenosine triphosphatase in gastric parietal cells, the PPIs are considered the mainstay therapeutic reagents for a variety of acid-related disorders, including gastric and duodenal ulcer, reflux esophagitis and Zollinger-Ellison syndrome.[3]

As a substitute for benzimidazole, lansoprazole is structurally related to omeprazole, and has asymmetric sulfur in its chemical structure. It is clinically administered as a racemic mixture of R^+- and S^--enantiomers. Lansoprazole is extensively metabolized in the human liver to 5-hydroxylansoprazole and lansoprazole sulfone.[4,5] The sulfoxidation of lansoprazole is catalyzed by CYP3A4, while its hydroxylation is catalyzed by CYP2C19 at lower concentrations and CYP3A4 at higher concentrations.[6,7]

Several studies have consistently revealed that the area under the plasma concentration-time curve (AUC) in poor metabolizers (PMs) was much bigger than those in extensive metabolizers (EMs).[8,9] CYP2C19 is predominantly involved in LPZ metabolism in EMs and CYP3A4 is predominant in PMs.[10] Therefore, patient CYP2C19 status is closely related to the clinically therapeutic outcomes.[11]

Although LPZ alone has a relatively low eradication effect on *Helicobacter pylori*, it may enhance the ability of other agents (clarithromycin and amoxicillin) to eradicate the organism.[10,12] A substantial number of studies have indicated that oral LPZ 30 mg/day provided effective symptom relief and healing of duodenal ulcer in 75~100% of patients after four weeks of therapy.[13] Nevertheless, the effect of LPZ on the intragastric pH is dependent on individual CYP2C19 genotype status.[14] Mutation in the CYP2C19 gene can influence the plasma concentration-time curve and the intragastric pH.[15] PMs show greater inhibition of gastric acid secretion because of the delayed metabolism. In contrast, due to the high CYP2C19 enzyme activity in EMs, LPZ is rapidly metabolized and less effective at inhibiting gastric acid secretion.

Intravenous (iv) formulations of the lansoprazole are currently used for short-term treatment of erosive esophagitis and upper gastrointestinal bleeding in patients who are unable or have difficulty in swallowing oral formulations.[16] The extent of the dependence of the pharmacokinetic parameters on CYP2C19 status of patients receiving a multiple drug regimen is not yet fully understood. In order to evaluate the impact of CYP2C19 status on the LPZ intravenous administration in clinical therapy, we investigated the pharmacokinetics in healthy Chinese volunteers who were given single or repeated iv infusion of LPZ.

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Key words: CYP2C19 genotype, extensive metabolizers (EMs), lansoprazole, poor metabolizers (PMs), proton-pump inhibitors (PPIs).

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Materials and Methods

Study design and demographic characteristics of the study cohort

The protocol was approved in advance by the hospital ethics committee and conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. After receiving oral and written explanations of the study, subjects gave written informed consent prior to starting the study. All subjects (15 males and 15 females) were recruited randomly into three dosage (15, 30, 60 mg) groups. The volunteers, who had been given 30 mg single-dose, continued to receive successive iv infusion administration (30 min each time) from the second day, twice daily for seven days. None of the subjects consumed excessive amounts of alcohol or smoked, and none took or had taken any drugs during or for at least one week before the study. Subjects were excluded if they presented clinically significantly abnormal electrocardiogram, blood chemistry or urine analysis, or a positive pregnancy test. Demographic characteristics of the

study cohort are shown in Table 1. Subjects were fasted from ten hours before to two hours after LPZ administration. Lansoprazole sterile injection powder was provided by Jichuang Pharmaceutical Company Ltd., PR China.

Subjects and CYP2C19 genotypes

Blood samples were obtained prior to the administration of LPZ, and DNA was extracted from each volunteer's leukocytes using a commercially available kit (Takara Blood Genome DNA Extraction Kit; Takara Biotechnology (DALIAN), China). Genotyping procedures for identifying the CYP2C19 were performed by a PCR-restriction fragment length polymorphism method using allele-specific primers.[17,18] Two were homozygous for the wild-type alleles in both exon 5 and 4 (*1/*1) and were classified as homEMs. Another 18 subjects were heterozygous for the *2 mutation without *3 mutation (*1/*2) or were heterozygous for the *3 mutation without *2 mutation (*1/*3) and were classified as the hetEMs. The remaining 10 subjects were heterozygous for both the *2 mutation and *3 mutation (*2/*3) or homozygous for the *2 mutation without the *3 mutation (*2/*2) and were classified as the PMs (Table 1).

CYP2C19*17 genotyping was performed using allele specific (AS)-PCR for –806C>T, as described by Sim *et al.*[19] The first PCR reaction was carried out using primers P806-F and P806-R, yielding a fragment of approximately 470 bp. In the subsequent AS-PCR reaction, primer P806-WT or P806-MUT was used together with P806-R to discriminate between the –806C (wild-type) and –806T (mutant type) alleles, respectively. Both the wild-type and mutation reactions yielded a fragment of approximately 200 bp. Results show that none of the 30 subjects have SNP at position –806 (C>T) relative to translation start.

Sample collection and assays of rabeprazole

Peripheral blood samples were drawn from an iv cannula inserted into a forearm vein into 5-mL heparinized tubes prior to and after the iv administration of LPZ at the following times: 15, 30, 45, 60, 75, 105, 165, 225, 300, 390, 480, 600, 720 min. After collection, the blood samples were immediately centrifuged at 3500 rpm for 10 min, and the plasma was separated and stored at -70°C until analysis. Plasma levels were measured by HPLC with UV detector (LC-2010- CTH; Shimadzu, Japan). Rabeprazole (RPZ) was used as internal marker for each sample (RPZ and LPZ were supplied by the National Institute for the Control of Pharmaceutical and Biological Products, China). The assay was performed according to the following procedure: an aliquot of 0.5 mL of plasma was mixed with 200 μL of NaOH (0.001 mol/L) to alkalify the plasma, then 75 μL of the RPZ solution (10.0 μg/mL) was spiked and vortex-mixed with 4 mL of diethyl ether for 3 min to extract the analytes. The organic phase was transferred to a new tube and evaporated to dryness at 37°C. The residue was dissolved with 200 μL solvent (0.001 mol/L NaOH: acetonitrile at 60:40, v/v) and centrifuged at 4°C with 16000 rpm for 10 min. The supernatant was then filtered through a 0.45-μm filter. An aliquot of 20 μL of supernatant obtained was injected for analysis with a Kromasil 100-5C18 column (250×4.6 mm, 5 μm; EKA Chemicals, Sweden). The mobile phase consisted of deionized water, acetonitrile (Merck, Germany) and methanol (Merck) (50: 41: 9, v/v/v). The flow rate was 1.0 mL/min, the detector wave was 290nm. The limit of quantification was 10 ng/mL, and the intra- and inter-batch relative standard deviations were less than 8.5 and 12.0%, respectively.

Method validation: specificity (selectivity)

Representative RP-HPLC chromatograms of saliva samples are shown in Figure 1. Retention times were approximately 8.2 and 6.3 min for LPZ and RPZ, respectively. The peaks of interest were well separated and free from interference from endogenous substances.

Method validation: linearity and calibration curves

Calibration curves were constructed by plotting peak areas ratio (A_{LPZ}/A_{RPZ}) *versus* concentrations of LPZ, and the regression equations were calculated. Calibration curves were plotted over the concentration range of LPZ (10, 20, 50, 100, 250, 500, 1000, 2000, 4000 ng/mL). Each solution was assayed five times. The least-squares method was used for the calculation of slope, intercept and correlation coefficient (r). The limit of detection (LOD) was separately determined at a signal to noise ratio (S/N) of 3, with a R.S.D. value less than 15 %; LODs for LPZ were found to be 6.0 ng/mL (Table 2).

Method validation: extraction recovery

The extraction recovery (R) of mixtures at three concentration levels (20, 1000, 4000 ng/mL) was determined by comparing two different sets of samples. In set 1, blank plasma was spiked with the analytes and prepared as described in the sample preparation procedure, and the obtained peak areas ratio of the analytes was defined as A. In set 2, the analytes were resolved in extracting solution, which were obtained from blank plasma, and the obtained peak areas ratio of the analytes was defined as

Table 1. Demographic characteristics of subjects.

Category	15 mg	30 mg	60 mg
N. subjects	10	10	10
Sex (male/female)	5/5	5/5	5/5
Age (years)	31.4±7.6 (23-43)	31.3±5.1 (23-38)	32.4±7.1 (24-42)
Weight (kg)	58.4±7.1 (48-68)	62.4±6.7 (53-75)	60.4±8.2 (50-75)
Height (cm)	165.8±7.3 (158-178)	167.2±7.2 (156-180)	166.3±6.9 (153-175)
Body mass index	21.3±0.9 (19.1-22.5)	22.3±1.0 (21.0±24.0)	21.8±1.7 (19.1-23.8)
HomEM/HetEM/PM	0/7/3	1/5/4	1/6/3

HomEM, homozygous extensive metabolizer; hetEM, heterozygous extensive metabolizer; PM, poor metabolizer. Values are given as mean±SD (range).

Table 2. Results from regression analysis of the calibration curves, limit of quantification and limit of detection.

Linear regression equations	Correlation coefficient r	LOQ (ng/mL)	LOD (ng/mL)
f=0.00003+0.001×C	0.9998	10.0	6.0

LOD, limit of detection; LOQ, limit of quantification; f, A_{LPZ}/A_{RPZ} (Ratio of peak area of lansoprazole to that of rabeprazole).

Table 3. The extraction recoveries of lansoprazole (n=3).

Concentration (ng/mL)	Extraction recovery (%)
20	126.3±7.5
1000	113.1±1.4
4000	135.3±8.3

B. The extraction recovery was calculated using the formula: R (%)=A/B*100. The extraction recoveries of LPZ are shown in Table 3.

Method validation: precision and accuracy

The intra-day and inter-day precisions of the proposed methods were determined by estimating the corresponding responses for three different concentrations (20, 1050, 3840 ng/mL) of LPZ five times during the same day and over three consecutive days, respectively. The intra-day and inter-day precision was 12.8% or less for each level. The results demonstrate that the values were within the acceptable range and the method is accurate and precise.

Method validation: stability

The stability data from three concentration levels of 20, 1000, and 4000ng/mL demonstrate the suitability of the method. One portion of standard solutions was kept at room temperature for 2 h and another portion was stored under refrigeration at -20°C for 30 days. These were then compared with that of a freshly prepared solution. The results showed that it was stable in these studied conditions.

Data and statistical analysis

Data are expressed as the mean±standard deviation (SD). The pharmacokinetic parameters of AUC, elimination half-life ($t_{½}$) and total clearance (Cl_{total}) were calculated using the non-compartmental method with the aid of DAS 2.0 program (China). Statistical analyses were performed using the SPSS software for Windows (ver. 11.5). Statistically significant differences in the mean pharmacokinetic parameters between different CYP2C19 genotypes were determined by one-way analysis of variance (ANOVA) with an unpaired two-tailed heteroscedastic t-test. We used the paired t-test to compare the AUC, C_{max}, $t_{½}$ and Cl_{total} values from single to repeated doses. Statistical significance was set at $P<0.05$.

Results

The area under the plasma concentration-time curve and C_{max} values for lansoprazole in plasma

The mean values of $AUC_{0-\tau}$ in two different genotype groups which received single and repeated doses are shown in Figure 2A. After single dose of 15, 30 and 60 mg, the mean $AUC_{0-\infty}$ in PMs and EMs were (225.9±58.7) and (128.0±37.8), (387.5±111.7) and (232.6±59.1), (885.8±232.6) and (495.5±127.7) μg.min.L^{-1}, respectively. In each single dose group, the mean AUC of the PMs was significantly higher

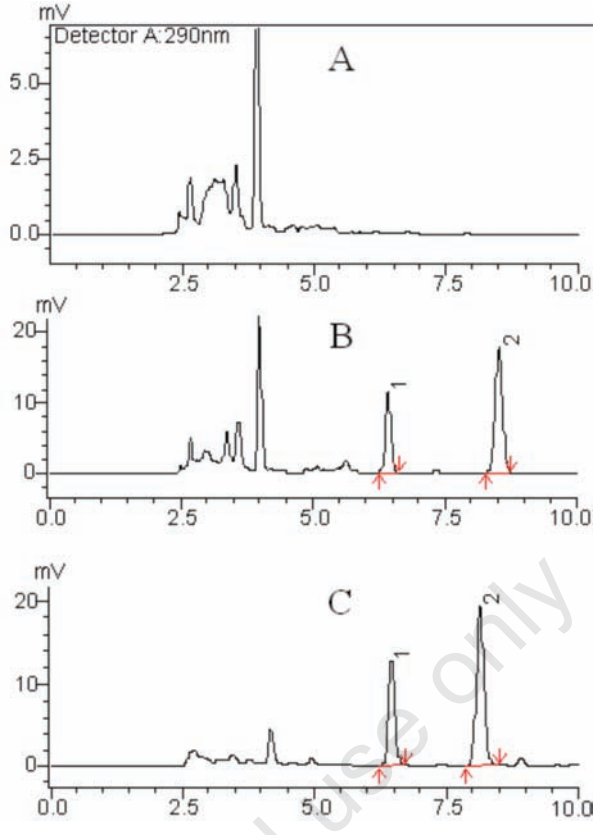

Figure 1. Typical chromatograms of (A) blank saliva, (B) blank plasma spiked with analyte controls, and (C) plasma sample after giving lansoprazole (1: RPZ; 2: LPZ).

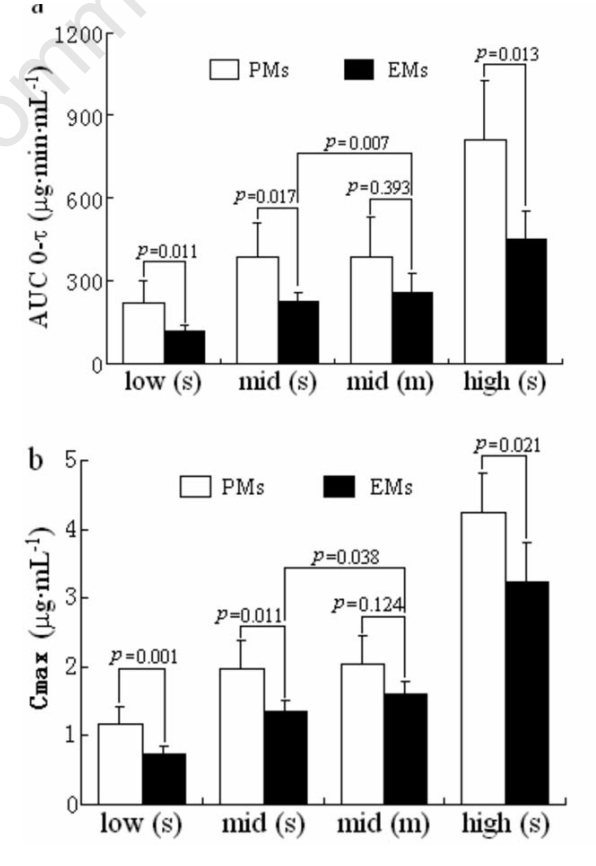

Figure 2. Mean $AUC_{0-\tau}$ and C_{max} values in different CYP2C19 genotypes after single (15, 30 and 60 mg) and repeated doses (30 mg) by iv infusion administered during a 60-min period, twice daily for seven days. The mean ±SD values are shown. low (s): 15mg single dose; mid (s): 30 mg single dose; mid (m): 30 mg multiple dose; high (s): 60 mg single dose. EMs, extensive metabolizers; PMs, poor metabolizers.

than that of the EMs. After repeated doses of 30 mg, the mean $AUC_{0-\infty}$ in EMs and PMs of the middle dose group were (391.6±121.6) and (269.1±66.3) μg.min.L^{-1}, respectively. The mean AUC ratios in PMs and EMs were 2.1:1 after a single dose of 30mg and were 2.2:1.4 after repeated dosing. This shows that the mean AUC increased significantly with the progression from single to multiple doses in EMs, while there was no significant increase in PMs.

The mean C_{max} in two different genotypes after single and repeated doses is shown in Figure 2B. In each single dose group, the mean C_{max} of the PMs was significantly higher than that of the EMs. The mean C_{max} ratios in PMs and EMs were 1.4:1 after a single dose of 30 mg and were 1.5:1.2 after repeated dosing. The mean C_{max} increased significantly from single to repeated doses in EMs, while there was no significant increase in PMs.

As shown in the linear equation and the scatter diagrams (Table 2 and Figure 3), the $AUC_{0-\tau}$ and C_{max} in three single-dose groups were linear over these doses (Table 4).

Elimination half-life (t) and total clearance (Cl_{total}) values in plasma

The mean $t_{½}$ in two different genotypes after single and repeated doses is shown in Figure 4A. A significant difference was observed between the two genotypes after a single dose of 15, 30 and 60 mg. The mean $t_{½}$ in PMs was significantly higher than that in EMs. The significantly increasing of mean $t_{½}$ in the progression from single to repeated doses was observed only in EMs but not in PMs.

The Cl_{total} in two different genotypes after single and repeated doses is shown in Figure 4B. In each dose group, the mean Cl_{total} in PMs was significantly lower than that in EMs. Although the mean Cl_{total} decreased significantly in the progression from single to repeated doses in EMs, no statistically significant decrease in PMs was observed.

Discussion

We observed that lansoprazole showed a linear increase in the plasma concentrations and AUC over a dose range of 15~60 mg by intravenous infusion. There was a significant difference in $AUC_{0-\tau}$ shown between the two different CYP2C19 genotypes after single dose treatment. The AUC of lansoprazole in PMs was significantly higher than that in EMs. In addition, we noticed that the relative value of the $AUC_{0-\tau}$ in PMs and EMs was 2.1:1 after a single dose of 30 mg LPZ and amounted to 2.2:1.4 after repeated dosing. There was no significant difference shown between single dose and multiple dose treatment in PMs, while there was a marginal increase in EMs from single to multiple doses.

The AUC value of lansoprazole in PMs has been reported to be more than four times higher than that in EMs by oral administration.[8,20] Our results show that the AUC value in PMs was 2.1-fold that of EMs when lansoprazole was administrated by intravenous infusion. One may wonder why the difference in AUC between the CYP2C19 genotypes after oral dosing is much greater than that of iv infusion. One possible explanation may be that the iv infusion was administered over a period of 60 min while the plasma concentrations were monitored for 12 h. On the other hand, when LPZ is administered orally in enteric capsule/tablet format, it normally takes 1.5-2.5 h to dissolve in the intestinal tenue while blood samples are collected at various time points up until 16-24 h.[5,11]

The mean $t_{½}$ of lansoprazole in our EM subjects was significantly increased and the mean Cl_{total} was significantly decreased after repeated doses, while there was no significant change in PMs. This result suggests that LPZ was more rapidly eliminated from the systemic circulation in EMs than in PMs. Although LPZ is mainly metabolized by CYP2C19, it can inhibit CYP2C19 activity after repeated doses because LPZ is a hepatic microsomal enzyme inhibitor.[10,21] This could partially explain why, after repeated doses, the mean AUC, C_{max}, and $t_{½}$ of the EMs increased significantly, while the mean Cl_{total} decreased significantly. Overall, the data obtained from different dosage levels and repeated doses indicate that the kinetic disposition of lansoprazole depends on individual CYP2C19 genotype status.

There is a considerable interethnic difference in the oxidation reaction in different pop-

Table 4. The relationship between ln C_{max} or ln $AUC_{0-\tau}$ and doses in different CYP2C19 genotypes. EMs, extensive metabolizers; PMs, poor metabolizers AUC, area under the plasma concentration-time curve.

Parameter	Genotype	Relationships	R	P	Linear correlation
ln C_{max}	PMs	ln C_{max} = 0.027D + 6.792	0.917	<0.0001	Significant
	EMs	ln C_{max} = 0.029D + 6.308	0.932	<0.0001	Significant
ln $AUC_{0-\tau}$	PMs	ln$AUC_{0-\tau}$=0.031D+ 11.834	0.798	<0.0001	Significant
	EMs	ln$AUC_{0-\tau}$= 0.03D + 11.214	0.909	<0.0001	Significant

D, doses; R, Adjusted R Square.

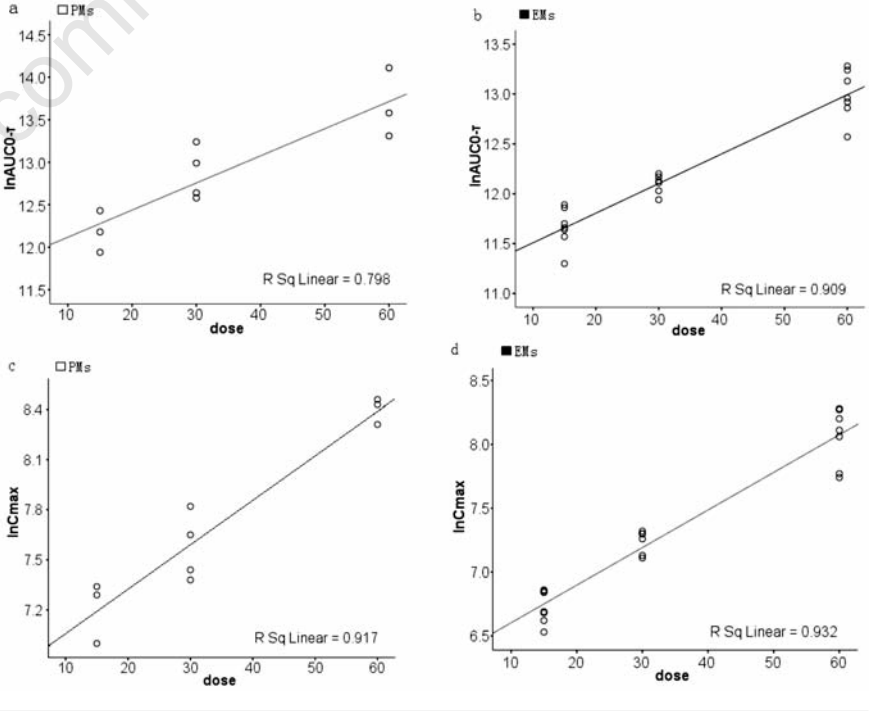

Figure 3. Scatter diagram of the relationship between dose and (A) AUC0-t in PMs, (B) AUC0-t in EMs, (C) C_{max} in PMs, and (D) C_{max} in EMs. EMs, extensive metabolizers; PMs, poor metabolizers AUC, area under the plasma concentration-time curve

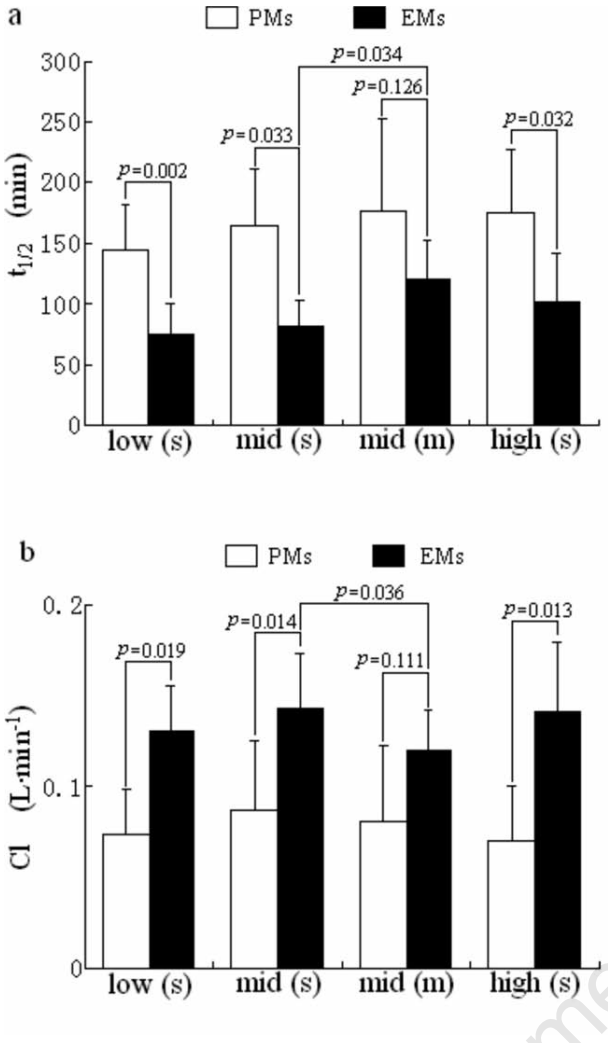

Figure 4. Mean half-life ($t_{1/2}$) and total clearance (Cl_{total}) in the different CYP2C19 genotypes after single (15, 30 and 60 mg) and repeated doses (30 mg) by iv infusion administered during a 60-min period, twice daily for seven days. The mean ±SD values are shown. low (s): 15 mg single dose; mid (s): 30 mg single dose; mid (m): 30 mg multiple dose; high (s): 60 mg single dose.

ulations. For example, 2-5% of Caucasians have been identified as carrying the PM phenotypes, whereas the PM frequency is 12.6-22.5% in the Asian population.[22] A novel allele (CYP2C19*17) with 2 SNPs in the 5'-flanking region that is associated with increased CYP2C19 activity *in vivo* have been found when comparing 2 different ethnic populations. The existence of the CYP2C19*17 allele may explain why some patients exhibit a lack of response to commonly prescribed dosages of certain PPIs. The unusually rapid clearance of the PPIs is caused by the CYP2C19*17 allele in those patients. The frequency of the CYP2C19*17 allele is equally high (18%) in Ethiopians and Swedes, but it is only 4% in Chinese subjects.[19,23] Based on the result of the genotype analysis, none of our 30 subjects has CYP2C19*17 mutation. The small number of subjects in our study may be seen as a limitation. A further study including a larger number of patients, especially those with acid-related diseases, will be carried out to further evaluate the impact of CYP2C19 on the pharmacokinetics of lansoprazole administered by intravenous infusion.

Conclusions

Our results indicate that CYP2C19 genotype could be a useful clinical tool to optimize the LPZ therapeutic dose. Therefore, the AUC and C_{max} values were most likely dependent on the CYP2C19 status of the individual.

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