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Effect of CYP2C19 Polymorphism on Treatment Success in Lansoprazole-Based 7-Day Treatment Regimen for Cure of *H. pylori* Infection in Japan

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Recently, *Helicobacter pylori* (*H. pylori*)-positive peptic ulcer patients were treated by a 1-week triple therapy [lansoprazole (LPZ) 30 mg, amoxicillin 750 mg and clarithromycin 200 or 400 mg, each twice daily] without the checking CYP2C19 genotype in Japan. This regimen was done to obtain sufficient cure rates for *H. pylori* infection using a high dose of LPZ (60 mg/day) without the great cost of having to determine the genotype. However, the failure rate for eradicating *H. pylori* was reported to be 12.5%. The reasons for this were studied in 33 Japanese patients with *H. pylori*-positive gastric or duodenal ulcer. Blood samples of the patients were collected to determine the genotype of CYP2C19 and plasma concentrations of LPZ and its metabolites at 3 h postdose on the morning of the 7th day of treatment. *H. pylori* infection was cured in 25 of the 33 patients (75.8%). The cure rate was highest in the group of poor metabolizers (PM), intermediate in the group of extensive metabolizers of the heterozygous type (htEM) and lowest in the group of extensive metabolizers of the homozygous type (hmEM). The relative ratio of mean plasma concentration for LPZ among the 3 groups was 1.00:1.43:2.93 (hmEM: htEM:PM groups). Our data suggest that success of the eradication is dependent on the CYP2C19-related genotypic status or the plasma concentrations of LPZ in a steady state condition after a multiple dosing regimen; that is to say, checking CYP2C19 is necessary even on occasions when treatment is done by *H. pylori* eradication methods as performed in Japan.

Key words: CYP2C19; *Helicobacter pylori*; Japan; lansoprazole

Abbreviations: CAM, clarithromycin; Cmax, maximal concentration; EM, extensive metabolizer; hmEM, homozygous EM; htEM, heterozygous EM; LPZ, lansoprazole; LPZ-SFN, lansoprazole sulfone; OH-LPZ, 5-hydroxylansoprazole; PM, poor metabolizer; PPI, proton pomp inhibitor; RFLP, restriction fragment length polymorphism

The prevalence of *Helicobacter pylori (H. pylori)* infection has increased with age in the Japanese. For Japanese born after 1950, the frequency of *H. pylori* infection increased at approximately 1% per year; for those born before 1950 the prevalence was high (70–80%) and relatively constant (Asaka et al., 1992). *H. pylori* infection was significantly more prevalent in Japanese than in Europeans and Americans (Schlemper et al., 1995). A high incidence of gastric cancer was reportedly related to infection with *H. pylori* (Parsonnet et al., 1991), and the highest incidence rates of gastric cancer in the world are found in Japan (Parkin et al., 2001). A high prevalence of the infection may portend continued high rates of gastric cancer in the forthcoming years (Uemura et al., 1997). Thus, it is highly important that *H. pylori* be eradicated in Japan.

There are many reports available regarding the predictive factors for successful treatment of *H. pylori*, and several host risk factors as well as bacterial factors are known to affect cure rates (Fallone et al., 1999; Kamada et al., 1999; Fujioka, 2000; Hoshiya et al., 2000). One recent report suggested that a polymorphism in the gene encoding the CYP2C19 enzyme for the proton pomp inhibitor (PPI) metabolism could affect the chance for a cure in *H. pylori*-positive patients who were treated with a 2-week dual therapy regimen with omeprazole and amoxicillin (Furuta et al., 1998). A recent trend for eradicating *H. pylori* involves the use of PPI-based triple therapies (Pounder, 1997; Unge, 1997) in order to obtain higher cure rates of eradication, while the impact of a CYP2C19 genetic polymorphism on the success of eradication in PPI-based triple therapies is still unclear.

Lansoprazole (LPZ) is a substituted benzimidazole derivative that effectively inhibits gastric acid secretion by irreversibly binding to the proton pump (H^+/K^+-ATPase) in gastric parietal cells (Sachs et al., 1995). LPZ is metabolized by a genetically determined S-mephenytoin 4'-hydroxylase [cytochrome P4502C19 (CYP2C19)] in the liver (Pearce et al., 1996). 5-Hydroxylansoprazole (OH-LPZ) and lansoprazole sulfone (LPZ-SFN) are the 2 major metabolites detectable in plasma (Pearce et al., 1996). An interindividual difference in the activity of CYP2C19 has been reported in relationship to the metabolic disposition of LPZ: in individuals with a poor metabolizer (PM) phenotype of CYP2C19, the area under the plasma concentration-time curve of LPZ is markedly increased (Sohn et al., 1997; Katsuki et al., 1997; Ieiri et al., 2001). Therefore, acid secretion in PMs of those who are undergoing LPZ therapy is assumed to be more strongly inhibited than in extensive metabolizers (EMs). The activity of CYP2C19 depends on CYP2C19 genotype status. Recently, Adachi et al. (2000) reported that the acid-inhibitory effect of LPZ was affected by CYP2C19 genotype status. Such studies suggest that the usual dose of LPZ for peptic ulcer (30 mg a day) may not attain therapeutically sufficient acid suppression in subjects who are homozygous EMs (hmEMs). In Japan, *H. pylori* eradication therapy was approved under the Japanese system of health insurance in November 2000. Since then, *H. pylori*-positive peptic ulcer patients were treated by a 1-week triple therapy (LPZ 30 mg, amoxicillin 750 mg and clarithromycin 200 or 400 mg, each twice daily) without checking for CYP2C19 genotypes in Japan (Satoh, 2002). The aim of this new regimen was to obtain high plasma concentrations of LPZ and sufficient cure rates for *H. pylori* infection using twice the dose of LPZ (60 mg a day) without the great cost for determining the genotype. This regimen showed that the *H. pylori* eradication rate was 87.5% in 2001 (Asaka et al., 2001); that is to say, the failure rate using this regimen for *H. pylori* eradication was 12.5%. The reasons for the failure have not been minutely analyzed so far. Accordingly, we conducted a prospective study in order to examine the reasons for the 1-week LPZ-based triple therapy regimen (LPZ 30 mg, amoxicillin 750 mg and clarithromycin 200 or 400 mg, each twice daily); for instance, we focused on i) the relationship between the CYP2C19 polymorphism and the plasma concentration of LPZ on the last day (=

steady state condition) of a 1-week triple therapy, ii) the relevancy between the CYP2C19 polymorphism and the cure rates of *H. pylori* infection, iii) existence of anti-biotic resistant *H. pylori*, iv) compliance status and v) other factors.

Subjects and Methods

The study samples were collected from 33 Japanese patients with gastric ulcer (n = 18) or duodenal ulcer (n = 15), who attended Tottori University Hospital or Toyooka Hospital. Twenty-seven patients were male and 6 were female; the mean age (± SD) was 56.8 ± 11.4 years. All patients had endoscopically proven gastric or duodenal ulcer and were positive for *H. pylori* based on plural evidence from rapid urease testing, culture, ^{13}C-urea breath testing and histologic examination.

For eradication of *H. pylori*, all patients received a 1-week triple therapy comprising LPZ 30 mg, amoxycillin 750 mg and clarithromycin 200 mg, all twice daily with food. Blood samples were collected to determine the genotype of CYP2C19 and blood concentrations of LPZ, OH-LPZ and LPZ-SFN at 3 h postdose on the morning of the 7th day which was after the beginning of drug administration for *H. pylori* eradication. We examined the blood concentrations of LPZ and its metabolites at 3 h postdose on the morning of the 7th day as parameters to estimate LPZ pharmacokinetics because the point of blood sampling was in a steady state of LPZ plasma concentration.

The blood samples were centrifuged and the plasma including LPZ and its metabolites were immediately collected. The plasma was stored at –20˚C until analysis. The concentrations of LPZ and its metabolites were determined by high performance liquid chromatography (Aoki et al., 1991).

Genomic DNA was prepared from blood samples using a DNA extractor WB kit (Wako, Osaka, Japan). The genotype CYP2C19 was identified using PCR-restriction fragment length polymorphism (PCR-RFLP) analysis as previously described (Ieiri et al., 2001; Kimura et al., 1998).

Patient adherence to therapy and occurrence of side effects were assessed by interview. Gastroduodenoscopy and determination of *H. pylori* infection were done before and 1 month after treatment. Endoscopists were uninformed of patient treatment status and genotypes. Written informed consent was obtained from each patient before the study began and our protocol was approved by the ethics review board of Tottori University Faculty of Medicine and Toyooka Hospital.

The susceptibility of each strain of *H. pylori* for clarithromycin was assessed in our laboratory at Tottori University Hospital by determining the minimal inhibitory concentration to the drug using an Etest (Aska Diagnostics, Tokyo, Japan).

Statistical differences in cure rates for *H. pylori* infection among the 3 genotype groups were determined by one-way analysis of variance and the Fisher exact test. Blood concentrations of LPZ, OH-LPZ and LPZ-SFN were analyzed for statistical differences using an unpaired t-test. A P value of less than 0.05 was considered to be statistically significant.

Results

No clinically undesirable signs or symptoms attributable to the therapy were noted during the entire study period. All patients completed the study according to protocol. Adherence to the prescribed medication regimen was 100% in all patients.

Subjects were genotypically classified into the 3 groups on the basis of PCR-RFLP analysis for CYP2C19 as shown in Table 1: homozygous EM group (hmEM), heterozygous EM (htEM) group and PM group.

H. pylori infection was cured in 25 of the 33 patients (75.8%). The cure rates of *H. pylori* infection for the 3 genotype groups are shown in

Table 1. Demographic and clinical characteristics of 33 patients with peptic ulcer in the 3 genotype groups

Variable	hmEM [11]	htEM [16]	PM [6]
CYP2C19 status	wt/wt	wt/m1† or wt/m2††	m1/m1‡ or m1/m2‡‡

EM, extensive metabolizer; hmEM, homozygous EM; htEM, heterozygous EM; PM, poor metabolizer; m1, CYP2C19 polymorphism in exon 5; m2, CYP2C19 polymorphism in exon 4; wt, wild-type.
[ ], number of patients.
† Heterozygous for CYP2C19m1 without CYP2C19m2.
†† Heterozygous for CYP2C19m2 without CYP2C19m1.
‡ Homozygous for CYP2C19m1 without CYP2C19m2.
‡‡ Heterozygous for both CYP2C19m1 and CYP2C19m2.

Table 2. The cure rate was the highest in the PM group, intermediate in the htEM group and the lowest in the hmEM group. The cure rate of the PM group was significantly higher than that of the hmEM group ($P < 0.05$).

The mean plasma concentrations of LPZ and its metabolites in relation to the 3 genotype groups are summarized in Table 3. These plasma concentrations (Table 3) were measured on the morning of the last day of therapy. An intergenotypic difference was observed for LPZ, OH-LPZ and LPZ-SFN described as follows: the relative ratio of mean plasma concentration for LPZ was 1.00:1.43:2.93 (hmEM:htEM:PM groups); the mean concentration of LPZ in the PM group was significantly higher than that in the hmEM or htEM group ($P < 0.05$); the relative ratio of mean plasma concentration was 1.00:0.78:0.47 for OH-LPZ and 1.00:5.19:15.71 for LPZ-SFN (hmEM:htEM:PM groups, respectively); and the mean concentration of LPZ-SFN in the PM group was significantly higher than that in the hmEM or htEM group ($P < 0.05$).

Cases in which eradication of H. pylori failed

Four patients (Patients 1 to 4) failed to be cured in the hmEM group (Table 4). Among the 4 patients, all strains of *H. pylori* were antibiotic-sensitive but the levels of plasma concentration of LPZ were not enough to eradicate *H. pylori*. Because the uptake of clarithromycin (CAM) into gastric tissue was enhanced in the case of a high-pH environment, keeping the intragastric pH at neutral levels by using acid-inhibitory agents such as LPZ may increase the availability of active antibiotics (Endo et al., 2001a, 2001b). So hmEMs are impeded in the eradication of *H. pylori*. Four patients (Patients 5 to 8) failed to be cured in the

Table 2. Cure rates of *Helicobacter pylori* infection in the 3 genotype groups

	Number of patients	Cure rate (%)
hmEM	11	7/11 (63.6%)
htEM	16	12/16 (75.0%)
PM	6	6/ 6 (100.0%)*

EM, extensive metabolizer; hmEM, homozygous EM; htEM, heterozygous EM; PM, poor metabolizer.
* $P < 0.05$ for the PM group compared with the hmEM group.

Table 3. Mean plasma concentrations of LPZ, OH-LPZ and LPZ-SFN on the morning of the last day of a 1-week triple therapy

Group	Number of patients	LPZ	OH-LPZ	LPZ-SF
hmEM	11	402.4 ± 156.7	31.0 ± 10.5	6.3 ± 4.5
htEM	16	573.7 ± 123.1	24.3 ± 6.4	32.7 ± 11.3
PM	6	1181.0 ± 247.8*	14.5 ± 7.7	99.0 ± 30.5†

EM, extensive metabolizer; hmEM, homozygous EM; htEM, heterozygous EM; LPZ, lansoprazole; LPZ-SFN, lansoprazole sulfone; OH-LPZ, 5-hydroxylansoprazole; PM, poor metabolizer.
Values are mean ± SEM (ng/mL).
* $P < 0.05$ for the PM group compared with the hmEM or htEM group.
† $P < 0.05$ for the PM group compared with the hmEM or htEM group.

Table 4. Antibiotics-sensitive status of *H. pylori* and plasma concentrations of LPZ, OH-LPZ and LPZ-SFN on the morning of the last day of a 1-week triple therapy in cases failured for *H. pylori* eradication

Group	Patient number	Plasma concentration (ng/mL)			Susceptibility
		LPZ	OH-LPZ	LPZ-SFN	Sensitive/resistant
hmEM	1	28	< 10	< 10	Sensitive
	2	149	24	< 10	Sensitive
	3	366	23	< 10	Sensitive
	4	84	21	< 10	Sensitive
htEM	5	807	53	< 10	Resistant
	6	636	69	40	Resistant
	7†	1107	< 10	150	Sensitive
	8	69	< 10	< 10	Sensitive
PM	All cases of PM were successful for *H. pylori* eradication. Mean plasma concentration of LPZ in the PM group was 1181.0 ng/mL as shown in Table 3.				

EM, extensive metabolizer; hmEM, homozygous EM; htEM, heterozygous EM; LPZ, lansoprazole; LPZ-SFN, lansoprazole sulfone; OH-LPZ, 5-hydroxylansoprazole; PM, poor metabolizer.
† Patient 7 had an unusual status of treatment for *H. pylori* eradication as shown in text.

htEM group (Table 4). The strains of *H. pylori* were antibiotic (CAM)-resistant in 2 (Patients 5 and 6) of the 4. The strain of *H. pylori* was antibiotic (CAM)-sensitive, but the level of plasma concentration of LPZ was not enough to eradicate *H. pylori* in 1 (Patient 8) of the 4.

Patient 7 (Table 4) had the following status for treatment of *H. pylori* eradication: i) 62 year old male, ii) drug compliance was good, iii) strain of *H. pylori* was antibiotic-sensitive, iv) no other disease except for peptic ulcer and v) level of concentration of LPZ was enough to eradicate *H. pylori*. This patient had treatment for *H. pylori* eradication twice. The 1st time was with the 1-week triple therapy (LPZ 30 mg, amoxicillin 750 mg and clarithromycin 200 mg, each twice daily) and the 2nd time was another 1-week triple therapy regimen (LPZ 30 mg, amoxicillin 750 mg and clarithromycin 400 mg, each twice daily). Neither method could produce any successful *H. pylori* eradication. On the other hand, all cases in the PM group were successful for *H. pylori* eradication (Table 4).

Discussion

Katsuki et al. (1997) have already reported on the relationship between CYP2C19 genotype status and metabolic disposition of LPZ using the single oral dose method (single oral administration of 30 mg LPZ) in Japanese subjects, and have shown that the hydroxylation of LPZ to OH-LPZ was apparently impaired in the PM. However, reports describing the relationship between CYP2C19 genotype status and metabolic disposition of LPZ using a multiple-dosing regimen are rare. In 2001, we planned a study using young healthy volunteers who were negative for *H. pylori* infection to provide preliminary information that should be considered when prescribing LPZ in a multiple-dose manner with reference to the CYP2C19-related genotype status (Ieiri et al., 2001). The healthy volunteers received 30 mg doses of LPZ once daily for 8 days and their pharmacokinetic parameters were measured using blood samples which were collected on the 8th day. The results showed that the relative ratio of the maximal concentration (Cmax) of LPZ was 1.00:1.29:2.00, that of OH-LPZ 1.00:1.20:0.20 and that of LPZ-

SFN 1.00:1.00:5.00 (hmEM:htEM:PM groups, respectively) on the 8th day. These data indicate the statistical differences of Cmax between any 2 genotypic groups among the 3 groups were not significant for LPZ; however, the differences of Cmax between the non-PM (hmEM and htEM) and PM groups were significant for OH-LPZ and LPZ-SFN ($P < 0.001$) (Ieiri et al., 2001).

In the present study, we observed the plasma concentration on the last day of a 1-week triple therapy for *H. pylori* eradication. The mean levels of plasma LPZ and LPZ-SFN in the PM group were significantly higher than those in the hmEM or htEM group after the multiple-dosing regimen. The relative ratio of mean plasma concentration was 1.00:1.43:2.93 for LPZ; 1.00:0.78:0.47 for OH-LPZ and 1.00:5.19:15.71 for LPZ-SFN (hmEM:htEM:PM groups, respectively). These differences of relative ratio on the 3 genotypic status after a multiple-dose regimen are clearer than those of our previous preliminary study using 30 mg doses of LPZ once a day for 8 days (Ieiri et al., 2001).

These differences in the 3 genotypic status which influence the plasma concentration of LPZ after a multiple-dose regimen are important, because the cure rates of *H. pylori* infection are different according to CYP2C19 genotype status as shown in Table 2. In Japan, *H. pylori*-positive peptic ulcer patients were treated with a 1-week triple therapy (LPZ 30 mg, amoxicillin 750 mg and clarithromycin 200 or 400 mg, each twice daily) without checking for the CYP2C19 genotype. The aim of this method was to obtain high plasma concentrations of LPZ and sufficient cure rates for *H. pylori* infection using two doses of LPZ (60 mg a day) without the great cost of determining the genotype. In this method, high eradication rates (84–91%) for *H. pylori* infection were found in gastroduodenal ulcer patients (Satoh, 2002). However, our data suggest that checking CYP2C19 is necessary even on the occasion of treatment by *H. pylori* eradication as it is done in Japan. The cure rate was highest (100.0%) in the PM group, intermediate (75.0%) in the htEM group and lowest (63.6%) in the hmEM group in the present study (Table 2); our data meant that the success of eradication was dependent on CYP2C19-related genotypic status or mean plasma concentrations of LPZ in a steady state condition, which is the morning of the last day on the 1-week triple therapy. In Japan, the prevalence of CAM-resistant *H. pylori* strains is about 10% to 20% (Satoh, 2002). Miki et al. (2003) reported that the key to successful eradication of *H. pylori*, using LPZ with CAM and amoxicillin, is CAM susceptibility, and not a CYP2C19 polymorphism. However, our results mentioned above indicate that not only administration of special antibiotics (for example, metronidazole) against CAM-resistant *H. pylori* strain but also CYP2C19-related genotypic status should be considered as a countermeasure in the failure of *H. pylori* eradication. Under the Japanese regimen for *H. pylori* eradication, we suggest that CYP2C19 genotyping should be done when *H. pylori* eradication fails, and then an adequate dose of LPZ should be administered to the patients; in addition to these treatments, checking the resistance ability of *H. pylori* against antibiotics is also important.

By the way, we experienced one case in which eradication of *H. pylori* failed notwithstanding the high level of plasma LPZ concentration, as in the PM group and antibiotic-sensitivity of the *H. pylori* strain (Patient 7 in Table 4). Wermeille et al. (2002) reported that poor compliance and bacterial resistance could only explain 40% of the failures in *H. pylori* eradication. Their report suggests that other factors must be involved. LPZ is known to be metabolized via CYP3A4 as well as CYP2C-19 (Pearce et al., 1996; Ishizaki and Horai, 1999). So CYP3A4 allelic variants may have been involved in the failure of the eradication in Patient 7 (Table 4). Several recent studies have reported that CYP3A4 allelic variants exist in Caucasian and African-American populations (Paris et al., 1999; Sata et al., 2000; van Schaik et al., 2000; Wandel et al., 2000). However, whether these isoform variants are associated with the altered metabolism of LPZ

appears to be controversial and conflicting (Sata et al., 2000; Wandel et al., 2000). Because the existence of CYP3A4-related PMs has not been reported in any part of the Japanese population so far, we did not examine CYP3A4-related phenotyping/genotyping factor(s) in the present study. On the other hand, there is also the possibility that other factors such as drug absorption or biological drug delivery/distribution may sometimes affect treatment success. Further examination is needed on these cases.

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