

Early effects of Lansoprazole orally disintegrating tablets on intragastric pH in CYP2C19 extensive metabolizers

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Abstract

AIM: To compare rabeprazole (RPZ; 10 mg) with Lansoprazole orally disintegrating tablets (LPZ; 30 mg OD) in terms of antisecretory activity and blood drug concentration after a single dose.

METHODS: Eight *H. pylori*-negative cytochrome P450 (CYP) 2C19 extensive metabolizers were assigned to receive a single oral dose of RPZ 10 mg or LPZ 30 mg OD. Twelve hour intragastric pH monitoring was performed on the day of treatment. Blood samples were also collected after the administration of each drug.

RESULTS: LPZ 30 mg OD induced a significantly earlier rise in blood drug concentration than RPZ 10 mg; consequently, LPZ 30 mg OD induced a significantly earlier rise in median pH in the third and fourth hours of the study.

CONCLUSION: In *H. pylori*-negative CYP2C19 extensive metabolizers, LPZ 30 mg OD induced a significantly faster inhibition of gastric acid secretion than RPZ 10 mg.

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Key words: LPZ 30 mg orally disintegrating tablets; Intragastric pH; Blood drug concentration; Cytochrome P450 2C19 extensive metabolizers; *H. pylori*-negative

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INTRODUCTION

Gastroesophageal reflux disease (GERD) is a common disease in the West^[1-3], with increasing prevalence in Japan^[4-7]. A recent study in Japan by Ohara *et al* has shown that a total of 42.2% of Japanese experienced heartburn^[6], which is a similar proportion to the estimated 42.4% reported in Western studies^[1]. Moreover, endoscopic studies have shown the overall prevalence of reflux esophagitis (RE) among the adult population of Japanese outpatients is 14%-16%^[4-7]. The mechanism of GERD is closely associated with gastric acid; thereby, gastric acid suppression is the most common therapeutic approach, and stronger and prompter gastric acid suppression is required^[8]. At present, drug therapy for reflux esophagitis is common because of its effectiveness; acid suppressing drugs such as H₂ receptor antagonist (H₂RA) and proton pump inhibitors (PPIs) are commonly used. As PPIs have been shown to be more effective against RE than H₂RA^[9-11], PPIs such as lansoprazole (LPZ) and rabeprazole (RPZ) are now widely used as first-line acid inhibitors. Continuous maintenance with PPIs is considered to be the mainstay of GERD treatment.

However, there are some reports not showing that all GERD patients need continuous acid inhibition. Bour *et al* reported that on-demand therapy with PPI provides an alternative to continuous therapy in patients with mild to moderate gastro-esophageal reflux^[12]. Several reports have

demonstrated that on-demand therapy with PPI provides an alternative to continuous therapy in patients with mild to moderate gastro-esophageal reflux^[13].

In Japan, many studies on RE have been done and although each report differs slightly, an obvious trend is apparent, showing most patients suffered from mild RE^[5-7], which is milder than that experienced in Western countries. As a result, some Japanese patients take PPIs when required according to their symptoms in the clinical setting.

It is reported that rapid acid suppression is important for effective pain relief at the onset of treatment in GERD patients^[14]. Thus, the aim of this study was to examine the correlation between pH value and blood drug concentration in patients treated with RPZ 10 mg or LPZ OD 30 mg at the early post-administration phase (1-12 h).

RPZ and LPZ are generally administered at doses of 10 mg or 30 mg, respectively, in the clinical setting in Japan. Thus, in the present study, the RPZ and LPZ doses were set at 10 mg and 30 mg, respectively.

Furthermore, in Japan many outpatients are administered multiple drugs. Hence, in order to improve drug compliance, RPZ and LPZ are also generally administered after a meal with other drugs. Therefore, we administered both RPZ and LPZ after a meal.

The acid-inhibitory effects of PPIs are significantly dependent on the cytochrome P450 (CYP) 2C19 genotype status, as well as on their intrinsic pharmacokinetic and pharmacodynamic characteristic and dosing schemes^[15-19]. According to these reports, the metabolism of PPIs is affected by the CYP2C19 polymorphism; the plasma PPI levels and intragastric pH values in extensive metabolizers are significantly lower than those in poor metabolizers^[20-22]. Therefore, in this study, the subjects were all CYP2C19 extensive metabolizers.

MATERIALS AND METHODS

Subjects

The subjects were 8 healthy male volunteers, aged between 24 and 48 years (median, 23 years) and weighing 52-78 kg (median, 54 kg). No patient had a history of gastrointestinal or hepatobiliary disease or of eradication therapy for *H pylori*, and none took regular medications. All volunteers gave written informed consent. The study protocol was approved by the ethical committee of the Tohoku University Graduate School of Medicine.

Detection of *H pylori* infection

H pylori infection was determined by the ¹³C-urea breath test^[23]. A total of 8 *H pylori*-negative subjects were invited and approved to participate in this study.

CYP2C19 genotyping

After obtaining informed consent, a venous blood sample was collected from all patients. DNA was extracted from the nucleus of venous white blood cells. The genetic mutation was analyzed by either the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method^[24] or the TaqMan polymerase chain reaction

amplification method (Applied Biosystems Japan, Chiba, Japan)^[25]. Based on point mutations in exons 4 and 5 of the CYP2C19 gene, individuals can be classified into homo-extensive metabolizers (homo-EMs), hetero-extensive metabolizers (hetero-EMs) and poor metabolizers (PMs)^[20-22]. Homo-EMs have the wild type alleles (wt/wt) without any mutations in exons 5 and 4; PMs have mutated alleles (m1/m2) with mutations in both exons 5 and 4 (m1/m2, m1/m1 or m2, m2); and hetero-EMs have a mutated allele in either exon 5 or 4 (wt/m1 or wt/m2).

Study protocol

All subjects (homo EM = 4, hetero EM = 4) participated in an open-label crossover study with RPZ 10 mg tablets or LPZ 30 mg OD. They were randomly assigned to receive a single oral dose of RPZ 10 mg tablet or LPZ 30 mg OD 30 min after eating a standardized meal. There was a washout period of at least 14 d between the two study periods. Twenty-four-hour intragastric pH monitoring was performed on the day of treatment. To monitor gastric pH, a pH electrode was inserted transnasally, and positioned fluoroscopically in the gastric corpus, approximately 5 cm-10 cm below the esophago-gastric junction. Gastric pH was measured at 10 s intervals by means of a portable pH meter attached to a glass pH electrode (Chemical Instrument, Tokyo, Japan). The pH electrode was calibrated before each recording, using standard buffers of pH 1.68, 4.01 and 6.86. The pH data were analyzed with the use of established software (Chemical Instrument). At fixed times (Breakfast 8:30 AM, lunch at noon, snack at 15:00 and dinner at 7:00 PM), standardized meals were consumed (total 1359 kcal; protein, 24 g lipid, 18.5 g glucose 267 g. The individual calorie contents of breakfast, lunch, snacks and supper were 356, 324, 355 and 324 kcal respectively). No additional food was allowed, and 100 mL of tap water was allowed only when the subjects felt thirsty. All subjects were instructed to remain upright until 21:00. Normal daily activities were not restricted.

Sample collection and assay of LPZ, RPZ concentration in plasma

In order to study the correlation between intragastric pH and blood drug concentration, blood samples were collected in heparinized tubes before and 0.5, 1, 1.5, 2, 3.5, 6, 9 and 12 h after the administration of each drug. After collection, the blood samples were immediately centrifuged at 3000 r/min for 10 min. For the determination of RPZ levels in plasma, 100 µL of 1% diethylamine solution was added to 1 mL of plasma; this was not required for the determination of plasma concentrations of LPZ. All samples were stored at -20°C until assayed. Plasma levels of LPZ and RPZ were measured by high-performance liquid chromatography/tandem mass spectrometry^[26,27]. This method required only 20 µL of serum and is a simple procedure. Analytes and the internal standard (lansoprazole deuterium derivatives) were separated using a mobile phase of acetonitrile/1 mmol/L ammonium formate (140/60, v/v) on a C18 analytical column and analyzed in the selected reaction-monitoring (SRM) mode. The lower limit of quantification was 500 fg/20 µL.

Table 1 Characteristics of the subjects in this study

Subject	CYP2C19	Age	Height (cm)	Body weight (kg)	BMI
1	Hetero	33	175	70	22.8
2	Hetero	50	175	73	23.8
3	Hetero	31	168	65	23.0
4	Hetero	22	165	60	22.0
5	Homo	31	168	65	23.0
6	Homo	26	173	68	22.7
7	Homo	23	171	70	23.9
8	Homo	25	184	75	22.1

Statistical analysis

Intragastric pH were expressed as median values (ranges). Differences in these parameters among each regimen were determined by the Wilcoxon signed rank test. *P* values less than 0.05 were considered significant.

RESULTS

Eight volunteers (all men; mean age 30.3 years, range years) completed the study. There were no adverse events during the study, which was completed according to the protocol by all 8 subjects. Four subjects were homo-EMs, and the other 4 subjects were hetero-EMs (Table 1).

The 12-h trendgram and the profiles of correlation between intragastric pH and blood drug concentration are shown in Figure 1. The lower limit for quantification of blood drug concentration was 500 fg/20 µL in this study. However, the blood drug concentration of RPZ was not detectable until 2 h after drug administration, while LPZ was detectable 0.5 h after drug administration. LPZ 30 mg OD induced a significantly earlier rise in blood drug concentration than RPZ 10 mg tablets.

As a result of this prompt rise in blood LPZ concentration, there was a prompt onset of median pH. The 12-h (median pH per hour) trendgrams of intragastric pH values obtained without medication are shown in Figure 1.

The intragastric pH values increased significantly with both drugs. LPZ 30 mg OD increased the pH value after the second hour of the study, while RPZ 10 mg tablets increased the pH value after the fourth hour of the study, compared with those pH values of individuals without medication.

LPZ 30 mg OD induced a significantly earlier rise in median pH in the third and fourth hours of the study than RPZ 10 mg tablets (Figure 1).

DISCUSSION

PPIs, such as omeprazole, LPZ and RPZ, are widely used for the treatment of acid-related diseases. The frequency of GERD has increased recently, because of increased average fat intake^[28], increased rates of obese patients^[29,30], and declining rates of *H. pylori* infection^[31,32]. GERD is a common disease in the West^[1-3] and appears to be increasing in prevalence in Japan^[4-7]. Recent endoscopic studies have shown overall prevalence of reflux esophagitis among the adult population in Japan is 14%-16%^[5-7]. Each report differs slightly, but an obvious trend is that

most patients suffer from mild RE^[5-7]. Moreover, it is reported that the incidence of atrophic gastritis in the general population is higher in Japan than in Western countries^[33-35], and that gastric acid secretion levels in the general population are lower in Japan than in Western countries^[33-36]. Thereby, some patients in Japan want administration of the drug on demand.

Patients with GERD mainly suffer of intermittent symptoms rather than continuous symptoms^[37]. On-demand therapy with PPIs is reported to provide an alternative to continuous therapy in patients with mild to moderate gastro-esophageal reflux disease suffering from frequent symptomatic relapse^[12].

It is important to use medicines that immediately ameliorate the clinical symptoms. Therefore, it is useful to administer antisecretory drugs which have a faster and stronger onset of pH rise in the stomach among patients with acid-related disorders.

Thus, we studied the effect in the early post-administration phase (1-12 h) of a single dosing of each PPI. In this study, LPZ 30 mg OD induced a significantly earlier rise in blood drug concentration than RPZ 10 mg tablets.

As a result of this prompt rise in blood LPZ concentration, LPZ 30 mg OD induced a significantly earlier rise in intragastric pH values compared with the values in individuals without medication after the second hour of the study, while RPZ 10 mg tablets induced an earlier rise in the fourth hour of the study. Moreover, LPZ 30 mg OD also induced prompt and stronger inhibition of gastric acid secretion than RPZ 10 mg tablets in the early post-administration phase, in the third and fourth hours following a single oral dose of treatment.

These results differ slightly from those of previous reports^[17-19,38,39] in which RPZ induced an earlier rise in intragastric pH than other PPIs. However, most previous studies examined the effects after administration of RPZ or other PPIs on days 3-7^[17-19,38,39], not at the early post-administration phase (1-12 h) of a single dose of treatment, whereas the present study examined the effect in this phase.

There are interindividual variations in the metabolism of PPI, resulting in differences in the acid-suppressing effect of each PPI^[17-19,38,39]. Each report differs slightly, but CYP2C19 genotype status is shown to influence gastric acid suppression by LPZ and most other PPIs. The metabolism of LPZ, OPZ and other PPIs is affected by the CYP2C19 polymorphism, and the plasma PPI level and intragastric pH values of EMs are significantly lower than those of PMs^[20-22]. On the other hand, several studies have demonstrated that after a dose of RPZ, intragastric pH is not affected by the CYP2C19 polymorphism on 3 d-7 d of treatment^[17-19,38,39]. However, Horai *et al.*^[15] reported the pharmacodynamic effects and pharmacokinetics of RPZ depend on the CYP2C19 genotype status on the first day after a single dose. As the present study is on the effect on the first day after a single dose of PPIs, both RPZ and LPZ are considered to be influenced by CYP2C19 genotype status.

Previous reports have indicated that *H. pylori* infection of the gastric mucosa potentiates the effects of proton pump inhibitors^[40,41]. Therefore, in the present study, the study subjects were all *H. pylori*-negative CYP2C19 EMs.

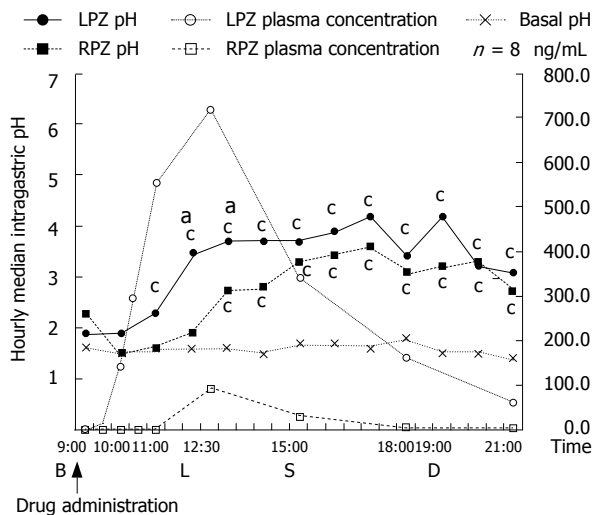


Figure 1 The 12-h (median pH per hour) trendgrams for all subjects ($n = 8$) and correlations with the blood concentration of each drug. The solid line (●) shows hourly intragastric median pH of individuals administered LPZ 30 mg OD, and the broken line (■) shows that of individuals administered RPZ. The solid line (○) shows the blood drug concentration level in individuals administered LPZ OD 30 mg, and the broken line (□) shows those in individuals administered RPZ 10 mg tablets. The solid line (x) shows the intragastric pH values of all subjects obtained without medication. LPZ 30 mg OD induces an earlier rise in both blood concentration level and median pH than RPZ 10 mg tablets. Arrows: Drug administration. B: Breakfast, L: Lunch, S: Snacks, D: Dinner. Blood sample were collected 1, 1.5, 2, 3.5, 6, 9 and 12 h after the administration of each drug. The significance of differences in these intragastric pHs among each regimen was determined by the Wilcoxon signed rank test. * $P < 0.05$ vs RPZ; † $P < 0.05$ vs baseline data.

Thus, we clearly state that LPZ 30 mg OD induces a significantly earlier rise in intragastric pH and stronger inhibition of gastric acid secretion than RPZ 10 mg tablets in the early post-administration phase (1-12 h) of a single dose of treatment.

Pipkin *et al* reported that rapid acid suppression is important for effective pain relief at the onset of treatment in GERD patients^[14]. Thereby, our results perhaps show that administration of LPZ 30 mg OD as an on-demand therapy is useful for mild GERD patients, because of its faster onset of pH rising action.

So why does LPZ 30 mg OD induce a prompt rise in intragastric pH than RPZ 10 mg tablets? This may be partly because of the difference between the dosage forms of RPZ and LPZ. In this study, we compared an enteric-coated tablet formulation of RPZ 10 mg tablets with an enteric-coated microgranule formulation of LPZ OD 30 mg in terms of antisecretory activity and the onset of action of a single dose.

PPIs are degenerated by gastric acid; therefore, for immediate passage through the stomach, some PPIs are formulated as granules or microgranules. This is necessary to ensure their intact passage through the stomach to allow for absorption in the intestine. The discharge speed, namely passage over time through the stomach, depends upon the particle diameter^[42-45].

According to physiological reports^[42-46], complexes of high amplitude action potentials occur in the stomach and duodenum. The interdigestive complex in the dog is looked upon as a “housekeeper”, which sweeps the

bowel clear of contents at the end of the digestive phase. Using a test food labeled with radionuclide, Davis SS *et al*^[46] reported that food emptied into the duodenum immediately, consisting of particles smaller than 2 mm without a “housekeeper”. Moreover, particles larger than 2 mm emptied into the duodenum after the “housekeeper,” which occurs after all meals have emptied from the stomach.

As a result, particles smaller than 2 mm empty from the stomach faster than particles larger than 2 mm. LPZ OD particles are smaller than 2 mm; thereby they may passage through the stomach into the duodenum and small intestine faster than RPZ, which is larger than 2 mm. They are absorbed in the small intestine and reach the gastric parietal cells *via* systemic circulation, where they bind to the proton pump, thereby resulting in potent acid inhibition^[16]. In fact, the plasma concentration level of LPZ 30 mg OD induced a prompt effect than RPZ 10 mg tablets, and consequently, LPZ 30 mg OD induced a prompt rise in intragastric pH than RPZ 10 mg tablets. These findings suggest that LPZ 30 mg OD is suitable for administration as an on-demand PPI, because of the prompt rise in plasma concentration level and the faster rise in intragastric pH.

In conclusion, LPZ 30 mg OD induced a significantly earlier rise in plasma concentration level in the early post-administration phase of a single oral dose than RPZ 10 mg tablets. As a result, LPZ 30 mg OD induced a significantly earlier rise in median pH in the early post-administration phase of a single oral dose than RPZ 10 mg tablets.

COMMENTS

Background

The prevalence of gastroesophageal reflux disease (GERD) symptoms is now increasing in Japan. GERD has a high rate of relapse. The rising use of proton pump inhibitor (PPI) therapy on demand has raised issues regarding efficacy.

Research frontiers

To compare RPZ 10 mg to LPZ 30 mg OD in terms of their antisecretory activity and blood drug concentration in the ultra-early phase after a single dose.

Innovations and breakthroughs

Most previous studies have examined pH monitoring after administration of PPI on days 3-7, not at the early post-administration phase.

Applications

We clearly state that LPZ 30 mg OD induced a significantly earlier rise in intragastric pH and stronger inhibition of gastric acid secretion than RPZ 10 mg tablets during the early post-administration phase (1-12 h) of a single dose of treatment. It is reported that rapid acid suppression is important for effective pain relief at the onset of treatment in GERD patients. Thereby, our results show administration of LPZ 30 mg OD as an on-demand therapy might be useful for mild GERD patients because of its faster onset of pH rising action.

Peer review

In this manuscript, the authors ascertained the effectiveness of LPZ 30 mg OD compared with RPZ 10 mg in the elevation of intragastric pH in the ultra-early state after a single oral administration. The study was well performed and the conclusion was clinically useful.

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