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Early effects of oral administration of omeprazole and roxatidine on intragastric pH

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Abstract: Objective: The ideal medication for the treatment of acid-related diseases, e.g., peptic ulcers, stress-related gastric bleeding, functional dyspepsia, and gastroesophageal reflux disease, should have a rapid onset of action to promote hemostasis and relieve the symptoms. The aim of our study was to investigate the inhibitory effects on gastric acid secretion of a single oral administration of a proton pump inhibitor, omeprazole 20 mg, and an H_2-receptor antagonist, roxatidine 75 mg. Methods: Ten *Helicobacter pylori*-negative male subjects participated in this randomized, two-way crossover study. Intragastric pH was monitored continuously for 6 h after single oral administration of omeprazole 20 mg and roxatidine 75 mg. Each administration was separated by a 7-d washout period. Results: During the 6-h study period, the average pH after administration of roxatidine was higher than that after administration of omeprazole (median: 4.45 vs. 2.65; P=0.0367). Also during the 6-h study period, a longer duration of maintenance at pH above 2, 5, and 6 was observed after administration of roxatidine 75 mg than after administration of omeprazole 20 mg (median: 90.6% vs. 55.2%, P=0.0284; 43.7% vs. 10.6%, P=0.0125; 40.3% vs. 3.3%, P=0.0125; respectively). Conclusions: In *Helicobacter pylori*-negative healthy male subjects, oral administration of roxatidine 75 mg increased the intragastric pH more rapidly than that of omeprazole 20 mg.

Key words: Proton pump inhibitor, H_2-receptor antagonist, Intragastric pH, Omeprazole, Roxatidine
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1 Introduction

The ideal medication for acid-related diseases, especially peptic ulcer, stress-related gastric bleeding, functional dyspepsia, and gastroesophageal reflux disease (GERD), should have a rapid onset of action in decreasing the intragastric acidity, because in-vitro studies have shown that blood coagulation and platelet aggregation are abolished at a pH less than 5.4 (Green *et al.*, 1978). Multiple agents, including antacids, H_2-receptor antagonists, and proton pump inhibitors, are currently available. Proton pump inhibitors are the most potent inhibitors of gastric acid secretion when used regularly (Burget *et al.*, 1990). However, a few studies have compared the time course of the effects of single oral dose administration of proton pump inhibitors and H_2-receptor antagonists.

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We designed this crossover study to compare the acute effects of single oral administration of omeprazole 20 mg and roxatidine 75 mg on intragastric pH.

2 Materials and methods

2.1 Subjects

This was a randomized, two-way crossover study of 10 healthy male volunteers with a mean age of 29.1 years (range: 23–44 years), who were not using acid-suppressive medications including antacids, H_2-receptor antagonists, and/or proton pump inhibitors. All subjects were negative for anti-*Helicobacter pylori* immunoglobulin G (IgG) antibodies (SRL Inc., Tokyo, Japan).

2.2 Study protocol and pH-metry

In this crossover study, all subjects received a single oral dose of omeprazole 20 mg (AstraZeneca Pharmaceutical Co. Ltd., Osaka, Japan) and a single oral dose of roxatidine 75 mg (ASKA Pharmaceutical Co. Ltd., Tokyo, Japan) in a random sequence. The drugs were administered with a washout period of at least 7 d between the two administrations. The subjects were requested to fast overnight (at least 8 h) before the treatment and also during a period of 6 h after the drug administration, and both drugs were given in the morning.

The pH electrode was inserted transnasally under local anesthesia and located in the body of the stomach. The gastric pH was measured at 10-s intervals with a portable pH meter equipped with an antimony pH electrode (Chemical Instrument Co. Ltd., Tokyo, Japan). The pH electrode was calibrated before each recording using standard buffers of pH 4.01 and 6.86. The pH data were analyzed using established software (Chemical Instrument Co. Ltd., Tokyo, Japan). The average pH and the percentage duration of the 6-h monitoring period over which the intragastric pH remained above 1.0, 2.0, 3.0, 3.5, 4.0, 5.0, 6.0, 7.0, and 8.0 after each drug administration were also measured (Iida *et al*., 2009).

2.3 CYP2C19 genotyping

DNA samples were obtained from white blood cells separated from whole blood samples obtained from the 10 subjects. The *S*-mephenytoin 4′-hydroxylase (CYP2C19) genotype was determined by polymerase chain reaction (PCR)-restriction fragment length polymorphism analysis (Kubota *et al.*, 1996). There are two point mutations of CYP2C19: the wild-type allele has G at position 636 in exon 4 and G at position 689 in exon 5; one of the mutated alleles (m1 allele) has A at position 689 in exon 5, and the other mutated allele (m2 allele) has A at position 636 in exon 4 (de Morais *et al.*, 1994a; 1994b). The CYP2C19 genotyping was performed by SRL Inc., Tokyo, Japan (Abe *et al*., 2004).

2.4 Statistics

Statistical evaluation was carried out using the Wilcoxon signed-rank test. The level of significance was set at $P<0.05$. The statistical analyses were performed using the Stat View program (SAS Institute, Cary, NC, USA).

2.5 Ethics

The study was conducted in accordance with the Declaration of Helsinki, and with the approval of the Ethics Committee of Yokohama City University School of Medicine, Japan.

3 Results

3.1 Adverse events

All subjects completed the study. No adverse events were recorded during the study.

3.2 Average pH

The average pH during the 6-h study period after administration of roxatidine 75 mg was higher than that after administration of omeprazole 20 mg (median: 4.43 vs. 2.65, respectively; P=0.0367) (Fig. 1).

The average pH was significantly higher after administration of roxatidine 75 mg as compared with that after administration of omeprazole 20 mg, in all the time periods measured: 0–1 h (median: 2.20 vs. 1.45; P=0.0380); 0–2 h (median: 3.80 vs. 1.85; P=0.0068); 0–3 h (median: 4.55 vs. 2.65; P=0.0189); 0–4 h (median: 4.65 vs. 2.65; P=0.0077); 0–5 h (median: 4.70 vs. 2.75; P=0.0189) (Fig. 2).

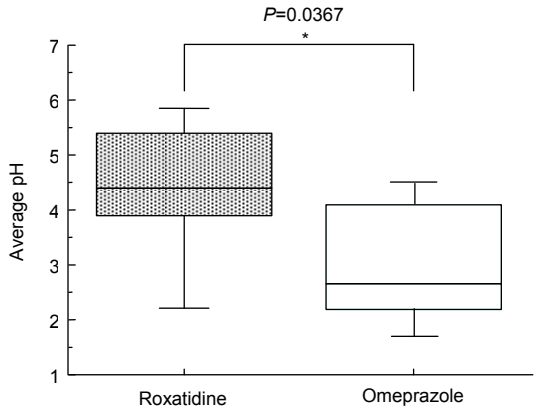

Fig. 1 Average pH during the first 6 h

Average pH during the first 6 h after administration of roxatidine was higher than that after administration of omeprazole. * P=0.0367 by the Wilcoxon signed-rank test

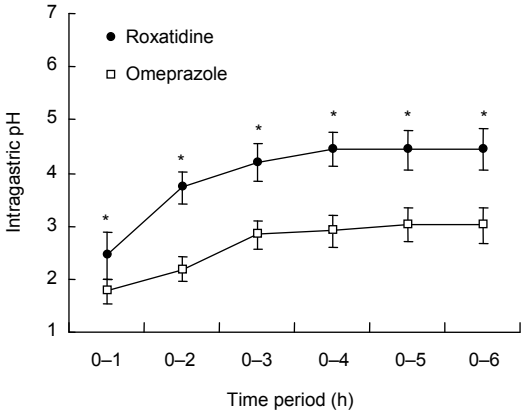

Fig. 2 pH profile during the first 6 h

A higher average pH was obtained at 0–1, 0–2, 0–3, 0–4, 0–5, and 0–6 h after administration of roxatidine 75 mg than after administration of omeprazole 20 mg. Circles (roxatidine) and squares (omeprazole), mean values; vertical line, standard error (SE); horizontal line, ±SD. * P<0.05 by the Wilcoxon signed-rank test

3.3 Holding time of various pH levels for over 4 h

During the 6-h study period, a longer duration of maintenance at pH above 2, 5 and 6 was observed after administration of roxatidine 75 mg as compared with that after administration of omeprazole 20 mg (median: 90.6% vs. 55.2%, P=0.0284; 43.7% vs. 10.6%, P=0.0125; 40.3% vs. 3.3%, P=0.0125; respectively) (Fig. 3).

3.4 CYP2C19 genotype

The results of CYP2C19 genotyping revealed nine subjects to be extensive metabolizers, including four homozygous extensive metabolizers with two wild-type alleles, and five heterozygous extensive metabolizers with one wild-type allele and one mutated allele; the remaining one subject was determined to be a poor metabolizer, with two mutated alleles.

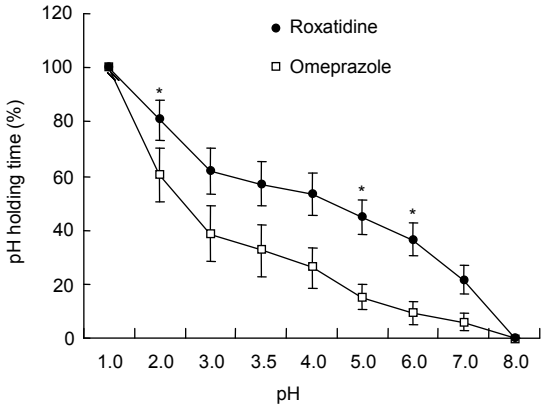

Fig. 3 pH holding time during the first 6 h

During the 6-h study period, a longer duration of maintenance at pH above 2, 5, and 6 was observed after administration of roxatidine 75 mg than after administration of omeprazole 20 mg. Circles (roxatidine) and squares (omeprazole), mean values; vertical line, standard error (SE); horizontal line, ±SD. * P<0.05 by the Wilcoxon signed-rank test

After administration of omeprazole and roxatidine, the average pH values during the 6-h study period were 2.8 and 3.9 in the homozygous extensive metabolizers, 2.4 and 5.0 in the heterozygous extensive metabolizers, and 4.2 and 4.5 in the poor metabolizers (median values).

4 Discussion

In this study, we examined the change of intragastric pH after a single oral administration of omeprazole 20 mg and roxatidine 75 mg, in the early post-administration phase, in *Helicobacter pylori*-negative subjects. We observed that roxatidine had a significantly faster onset of action and produced a stronger inhibition of intragastric acid secretion than omeprazole. These study results support the previous reports (Hurlimann *et al*., 1994; Chassany *et al*., 1996; Arnestad *et al.*, 1997; Hedenstrom *et al.*, 1997; Khoury *et al.*, 1999; Abe *et al*., 2004; Inamori *et al*., 2005; Iida *et al*., 2009) that H_2-receptor antagonists

increase intragastric pH more rapidly than proton pump inhibitors.

We selected omeprazole for study, among various currently available proton pump inhibitors, for several reasons. First, omeprazole has been used for over 20 years and is one of the most used drugs in Japan. Second, omeprazole 20 mg has been indicated for both initial therapy and maintenance therapy.

Roxatidine was discovered as an H_2-receptor antagonist in Japan (Tarutani *et al.*, 1985) and is used to treat peptic ulcer, functional dyspepsia, and gastroesophageal reflux disease. Roxatidine blocks gastric acid secretion and it has been shown to be approximately six-fold more potent than cimetidine in the inhibition of gastric acid secretion (Tarutani *et al*., 1985). In addition, roxatidine has been demonstrated to accelerate mucus secretion in animals and human (Ichikawa *et al*., 1999; Saito *et al*., 2000).

Omeprazole is inactivated by CYP2C19, while roxatidine is eliminated via the urine. Significant differences of acid secretion have been shown between extensive and poor metabolizers of CYP2C19 (Andersson, 1996; Williams *et al*., 1998; Furuta *et al*., 1999; Shirai *et al*., 2001; Saitoh *et al*., 2002). The frequency of the poor metabolizer phenotype of CYP2C19 shows variations: only 2% to 6% of Whites, as compared with 19% to 23% of Japanese (Wedlund *et al*., 1984; Kubota *et al*., 1996; Ishizaki and Horai, 1999). One of the 10 subjects (10%) in our study was identified to be a poor metabolizer.

The present results are also supported by the results of an in vitro study. In an autoradiographic study, Nakamura *et al*. (1995) reported that H_2-receptor antagonists accumulated equally on the parietal cells, while proton pump inhibitors accumulated only on young activated parietal cells. Nakamura *et al*. (1995) hypothesized that, because other proton pumps are quickly activated, the anti-secretory effect of proton pump inhibitors was not faster than that of H_2-receptor antagonists in the early phase post-administration.

Prophylactic treatment with oral H_2-receptor antagonists has been shown to reduce the bleeding rate (Moore, 1991; Smythe and Zarowitz, 1994), confirming the importance of raising the intragastric pH to prevent or treat stress ulcers. However, the intragastric pH necessary for protection against stress-related mucosal damage is not well established and, therefore, the optimal pH for the prevention of stress ulcers and bleeding is a subject for debate. Maintenance of the intragastric pH above 3.5 to 4.0 is thought to be necessary for preventing stress ulcers (Stothert *et al*., 1980; Frank *et al*., 1986; Watanabe *et al*., 1990), while an intragastric pH of over 6 is necessary for the treatment of existing stress ulcers (Fullarton *et al*., 1991). Our results show that a single oral administration of roxatidine produces a more rapid antisecretory effect as compared with omeprazole, and roxatidine may be suitable for initial therapy to promote hemostasis and for on-demand therapy in outpatients to relieve symptoms. On the other hand, omeprazole has more potent anti-secretory activity and is more effective than H_2-receptor antagonists in healing ulcers. This finding may be explained by studies that have shown that the anti-secretory activity of proton pump inhibitors increases progressively after repeated oral and intravenous administration, with a steady state achieved after about 5 d (Howden *et al*., 1984; Jansen *et al.*, 1988). In one study, a daily intravenous injection dose of proton pump inhibitors was not sufficient to maintain an intragastric pH (>4) during the first day of treatment (Jansen *et al*., 1988). However, after 5–7 d treatment, oral proton pump inhibitors were more effective than H_2-receptor antagonists in normal subjects, patients with duodenal ulcer, and those with GERD (Ohara *et al*., 1988; Ducrotté *et al*., 1994).

In conclusion, roxatidine 75 mg increases intragastric pH more rapidly than omeprazole 20 mg in *Helicobacter pylori*-negative subjects. This study shows that roxatidine 75 mg is more suitable for on-demand therapy to relieve symptoms than omeprazole 20 mg, when given as a single oral dose.

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