Inhibition of gastric perception of mild distention by omeprazole in volunteers

Akihito Iida, Hiroshi Kaneko, Toshihiro Konagaya, Yasushi Funaki, Kentaro Tokudome, Shinya Izawa, Yasuhiro Tamura, Mari Mizuno, Naotaka Ogasawara, Makoto Sasaki, Kunio Kasugai

Akihito Iida, Yasushi Funaki, Kentaro Tokudome, Shinya Izawa, Yasuhiro Tamura, Mari Mizuno, Naotaka Ogasawara, Makoto Sasaki, Kunio Kasugai, Division of Gastroenterology, Department of Internal Medicine, School of Medicine, Aichi Medical University, Aichi 480-1195, Japan
Hiroshi Kaneko, Department of Internal Medicine, Hoshigaoka Maternity Hospital, Aichi 464-0026, Japan
Toshihiro Konagaya, Marine Clinic, Nagoya, Aichi 460-0002, Japan

Author contributions: Iida A, Kaneko H, Konagaya T, Ogasawara N, Sasaki M, and Kasugai K designed the research; Iida A, Kaneko H, Konagaya T, Funaki Y, Tokudome K, Izawa S, Tamura Y, and Mizuno M performed the research; Iida A and Konagaya T analyzed the data; and Iida A and Kaneko H wrote the manuscript.

Supported by A Grant-in-Aid for Scientific Research from the Aichi Medical University Alumni Association, in part

Correspondence to: Akihito Iida, MD, PhD, Assistant Professor, Lecturer, Division of Gastroenterology, Department of Internal Medicine, School of Medicine, Aichi Medical University, 1-1 Yazakokarimata, Nagakute, Aichi 480-1195, Japan. iida@aichi-med-u.ac.jp
Telephone: +81-561-623311 Fax: +81-561-621508
Received: June 9, 2012 Revised: August 13, 2012
Accepted: August 25, 2012
Published online: October 21, 2012

Abstract

AIM: To evaluate the effects of omeprazole on gastric mechanosensitivity in humans.

METHODS: A double lumen polyvinyl tube with a plastic bag was introduced into the stomach of healthy volunteers under fluorography and connected to a barostat device. Subjects were then positioned so they were sitting comfortably, and the minimal distending pressure (MDP) was determined after a 30-min adaptation period. Isobaric distensions were performed in stepwise increments of 2 mmHg (2 min each) starting from the MDP. Subjects were instructed to score feelings at the end of every step using a graphic rating scale: 0, no perception; 1, weak/vague; 2, weak but significant; 3, moderate/vague; 4, moderate but significant; 5, severe discomfort; and 6, unbearable pain. After this first test, subjects received omeprazole (20 mg, after dinner) once daily for 1 wk. A second test was performed on the last day of treatment.

RESULTS: No adverse effects were observed. Mean MDP before and after treatment was 6.3 ± 0.3 mmHg and 6.2 ± 0.5 mmHg, respectively. One subject before and 2 after treatment did not reach a score of 6 at the maximum bag volume of 750 mL. After omeprazole, there was a significant increase in the distension pressure required to reach scores of 1 (P = 0.019) and 2 (P = 0.017) as compared to baseline. There were no changes in pressure required to reach the other scores after treatment. Two subjects before and one after omeprazole rated their abdominal feeling < 1 at MDP, and mean ± SE abdominal discomfort scores at MDP were 0.13 ± 0.09 and 0.04 ± 0.04, respectively. Mean scores induced by each MDP + 2, 4, 6, 8, 10, 12, 14, 16, 18 and 20 (mmHg) were 1.1 ± 0.3, 2.0 ± 0.4, 2.9 ± 0.5, 3.3 ± 0.4, 4.6 ± 0.3, 5.2 ± 0.3, 5.5 ± 0.2, 5.5 ± 0.3, 5.7 ± 0.3, and 5.4, respectively. After omeprazole, abdominal feeling scores for the same incremental pressures over MDP were 0.3 ± 0.1, 0.8 ± 0.1, 2.0 ± 0.4, 2.8 ± 0.4, 3.8 ± 0.4, 4.6 ± 0.4, 4.9 ± 0.3, 5.4 ± 0.4, 5.2 ± 0.6, and 5.0 ± 1.0, respectively. A significant decrease in feeling score was observed at intra-bag pressures of MDP + 2 mmHg (P = 0.028) and + 4 mmHg (P = 0.013), respectively, after omeprazole. No significant score changes were observed at pressures ≥ MDP + 6 mmHg.

CONCLUSION: Although the precise mechanisms are undetermined, the present study demonstrated that omeprazole decreases mechanosensitivity to mild gastric distension.
Inhibition of gastric perception of mild distention by omeprazole in volunteers. World J Gastroenterol 2012; 18(39): 5576-5580
Available from: URL: http://www.wjgnet.com/1007-9327/full/v18/i39/5576.htm DOI: http://dx.doi.org/10.3748/wjg.v18.i39.5576

INTRODUCTION

According to Rome III, the classification for functional gastrointestinal disorders published in 2006, functional dyspepsia (FD) is defined as the presence of one or more dyspepsia symptoms (postprandial fullness, early satiation, epigastric pain, or epigastric burning) that originate from the gastroduodenal region in the absence of any organic, systemic, or metabolic disease that is likely to explain the symptoms[1]. Alteration of gastric motility, visceral hypersensitivity, impaired accommodation of meals, gastritis induced by Helicobacter pylori (H. pylori) infection, and dysfunction of the central nervous system have all been implicated in the pathophysiology of FD[2-4]. Duodenal acidification increases proximal gastric mechanosensitivity, induces proximal gastric relaxation, and seems to inhibit the proximal gastric accommodation to a meal[5]. Hypersensitivity not only to acid in the duodenum but also gastric distension has been proposed among the possible mechanisms of FD. Thus, the mechanism by which decreased duodenal acid exposure affects symptoms of dyspepsia warrants investigation.

Omeprazole, a proton pump inhibitor that strongly decreases acid secretion, has been prescribed in the treatment of FD worldwide. This is the best first-line treatment when compared with ranitidine, cisapride, and placebo for primary care of H. pylori-negative dyspepsia patients[6-7]. However, changes in patients’ perceptions of gastric distention after omeprazole administration have yet to be clarified. The gastric barostat test has been reported to be the gold standard method for evaluating gastric perception[8,9]. In the present study, we examined the effects of omeprazole on mechanosensitivity in humans using the barostat test.

MATERIALS AND METHODS

Study subjects

Ten healthy volunteers were recruited (8 men, 2 women; mean age, 31.6 ± 2.1 years; range, 23 to 41 years). None of the subjects had any history of gastrointestinal dis-
RESULTS

No adverse effects were observed with omeprazole. Oral intubation with subsequent positioning of the barostat bag was well-tolerated by all subjects. The mean MDP before and after omeprazole was 6.3 ± 0.3 mmHg and 6.2 ± 0.5 mmHg, respectively. One subject at baseline and 2 after omeprazole did not reach discomfort scores of 6 at the maximum bag volume of 750 mL.

The distention pressures (mmHg) required to induce scores of weak/vague (score 1), weak but significant (score 2), moderate/vague (score 3), moderate but significant (score 4), severe discomfort (score 5), and unbearable pain (score 6) were 3.0 ± 0.5, 5.2 ± 0.7, 7.0 ± 1.0, 8.6 ± 0.9, 11.1 ± 0.8, and 13.5 ± 0.9, respectively, at baseline. After 1 week of daily omeprazole, the distention pressure required to induce the same scores (n = 10 for scores 1 to 4; n = 9, score 5; n = 8, score 6) were 4.6 ± 0.4, 7.8 ± 0.6, 9.4 ± 0.9, 10.4 ± 1.0, 13.8 ± 1.8, and 15.3 ± 1.0, respectively. The distended pressure needed to reach scores of 1 (P = 0.019) and 2 (P = 0.017) (Figure 1) increased significantly after omeprazole. No changes in pressure were demonstrated for other scores after treatment.

Eight subjects scored 0 for the MDP at baseline and 9 scored 0 for the MDP after omeprazole. The mean discomfort scores (±SE) at MDP before and after omeprazole were 0.13 ± 0.09 and 0.04 ± 0.04, respectively.

The mean scores induced by each MDP + 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20 mmHg were 1.1 ± 0.3 (n = 10), 2.0 ± 0.4 (n = 10), 2.9 ± 0.5 (n = 10), 3.3 ± 0.4 (n = 10), 4.6 ± 0.3 (n = 10), 5.2 ± 0.3 (n = 8), 5.5 ± 0.2 (n = 5), 5.5 ± 0.3 (n = 3), 5.7 ± 0.3 (n = 2), and 5.4 (n = 1), respectively. After omeprazole, the abdominal feeling scores for the same incremental pressures over MDP were 0.3 ± 0.1 (n = 10), 0.8 ± 0.1 (n = 10), 2.0 ± 0.4 (n = 10), 2.8 ± 0.4 (n = 10), 3.8 ± 0.4 (n = 10), 4.6 ± 0.4 (n = 10), 4.9 ± 0.3 (n = 8), 5.4 ± 0.4 (n = 5), 5.2 ± 0.6 (n = 3), and 5.0 ± 1.0 (n = 2), respectively. A significant decrease in the feeling score was observed at intrabag pressures of MDP + 2 mmHg (P = 0.028) and + 4 mmHg (P = 0.013), respectively, after omeprazole (Figure 2). No significant score changes were seen at pressures ≥ MDP + 6 mmHg.

DISCUSSION

In this study, we have shown for the first time the inhibitory effect of 1 wk of treatment with omeprazole on perception of mechanical distension by a barostat device. Namely, a significant increase was observed in the pressure required to induce a weak/vague feeling (score 1) and a weak but significant feeling (score 2). In other words, the perceived intensity of MDP + 2 and + 4 mmHg were significantly decreased after omeprazole treatment.

We recruited normal volunteers who were paid for their participation, and not all participants scored a weak/vague abdominal feeling (score 1) at intrabag pressure of MDP, indicating that the results obtained in the present study are limited to dyspepsia-free normal subjects.

The mechanisms by which omeprazole decreases perceptions of discomfort associated with gastric distension remain unknown. Omeprazole is a proton pump inhibitor that strongly decreases acid secretion. In a previous report of 5-d treatment with omeprazole at a similar dose (20 mg) to the present study, the number of hours with intragastric pH greater than 4 during a 24-h period was found to be 10.5 h[19]. Omeprazole has been reported to be most effective in patients who rated epigastric pain or heartburn as their most bothersome symptom[6,7]. Visceral hypersensitivity as well as gastric dysmotility, impaired accommodation to the meals, H. pylori-induced gastritis, and dysfunction of the central nervous system have all been implicated in the pathophysiology of FD[2-4]. Hypersensitivity to gastric distension and acid has especially been demonstrated in patients with FD. After the first report that gastric distension-induced perception was significantly increased in subjects with FD compared with controls in 1991[11,14], it has been reported that the hypersensitivity against distension might present in 34% to 66% of patients with FD[19]. In addition, duodenal acidification-
induced dyspeptic symptoms occur more significantly in patients with FD than in healthy volunteers. A growing set of evidence has clarified the role of acid on dyspeptic symptoms and mechanosensitivity. First, acid infusion into the stomach induced dysmotility-like predominant dyspeptic symptoms in healthy Japanese control subjects. Second, intraluminal infusion of hydrochloric acid affected sensitization of stomach mucosal mechanoreceptors. Finally, intraduodenal acid infusion increased fundic compliance, decreased the tone and phasic contractile activities of the fundus, and increased proximal gastric mechanosensitivity. These data suggest that the presence of acid in the upper gut might enhance mechanosensitivity. This putative mechanism has been supported by animal studies. Protons evoke multiple currents in primary afferent neurons that are carried by several acid-sensitive ion channels. Among these, acid-sensing ion channels (ASICs) and transient receptor potential vanilloid-1 (TRPV1) ion channels have been most thoroughly studied. Taken together, it is speculated that an omeprazole-induced decrease in acid secretion followed by the downregulation of chemoreceptors might suppress distension-induced mechanosensitivity, resulting in the reduced perception of gastric distension demonstrated in the present study.

In this study, the inhibitory effect of omeprazole on perception induced by intragastric bag distension was demonstrated only with mild distension stimulus and weak feeling in the abdomen in normal volunteers. The precise reasons for these limited effects are unclear. Jones et al demonstrated that both TRPV1 and ASIC3 knock-out mice were significantly less sensitive to colon distension, with an average response magnitude only 58% and 50% of controls, respectively. The data may suggest that afferent nociceptive signal transfer occurs mainly via a mechanoreceptor, rather than a chemo-receptor at moderate and severe distension.

It is well-known that gut infection is one of the risk factors for functional gastrointestinal disorders such as irritable bowel syndrome and FD. Visceral hypersensitivity after infection has been reported in both animals and humans. Proton pump inhibitors have been reported to have potential anti-inflammatory effects apart from acid suppression. Therefore, it is possible that the omeprazole-induced decreased perception of gastric distension might be mediated by the anti-inflammatory action of omeprazole.

In conclusion, although the precise mechanisms are undetermined, the present study demonstrated that omeprazole decreases mechanosensitivity to mild gastric distension, suggesting that the drug might be effective in the treatment of FD.

REFERENCES
1. Tack J, Talley NJ, Camilleri M, Holtmann G, Hu P, Malagelada JR, Stanghellini V. Functional gastroduodenal disorders. Gut 2006; 53: 1464-1479
2. Talley NJ, Choung RS. Whither dyspepsia? A historical perspective of functional dyspepsia, and concepts of pathogenesis and therapy in 2009. J Gastroenterol Hepatol 2009; 24 Suppl 3: S20-S28
3. Mimidis K, Tack J. Pathogenesis of dyspepsia. Dig Dis 2008; 26: 194-202
4. Oostmanakakis P, Tack J. Dyspepsia: organic versus functional. J Clin Gastroenterol 2012; 46: 175-190
5. Lee KJ, Vos R, Janssens J, Tack J. Influence of duodenal acidification on the sensorimotor function of the proximal stomach in humans. Am J Physiol Gastrointest Liver Physiol 2004; 286: G279-G284
6. Veldhuyzen van Zanten SJ, Chiba N, Armstrong D, Barkun A, Thomson A, Smyth S, Escobedo S, Lee J, Sinclair P. A randomized trial comparing omeprazole, ranitidine, cisapride, or placebo in helicobacter pylori negative, primary care patients with dyspepsia: the CADET-HN Study. Am J Gastroenterol 2005; 100: 1477-1488
7. Talley NJ, Meineche-Schmidt V, Paré P, Duckworth M, Räsänen P, Pap A, Kordecki H, Schmid V. Efficacy of omeprazole in functional dyspepsia: double-blind, randomized, placebo-controlled trials (the Bond and Opera studies). Aliment Pharmacol Ther 1998; 12: 1055-1065
8. Tack J, Piessevaux H, Couillie B, Caenepeel P, Janssens J. Role of impaired gastric accommodation to a meal in functional dyspepsia. Gastroenterology 1998; 115: 1346-1352
9. Tack J, Caenepeel P, Piessevaux H, Cuomo R, Janssens J. Assessment of meal induced gastric accommodation by a satiety drinking test in health and in severe functional dyspepsia. Gut 2003; 52: 1271-1277
10. Boeckxstaens GE, Hirsch DP, van den Elzen BD, Heisterkamp SH, Tytgat GN. Impaired drinking capacity in patients with functional dyspepsia: relationship with proximal stomach function. Gastroenterology 2001; 121: 1054-1063
11. Tutuian R, Vos R, Karamanolis G, Tack J. An audit of technical pitfalls of gastric barostat testing in dyspepsia. Neurogastroenterol Motil 2008; 20: 113-118

Iida A et al. Omeprazole decreases gastric perception

COMMENTS

Background
Hypersensitivity to gastric distension has been proposed among the possible mechanisms of functional dyspepsia (FD). Omeprazole has been prescribed in the treatment of FD. They examined the effects of omeprazole on mechanosensitivity in humans. The gastric barostat test is the gold standard method for evaluating gastric perception. They examined the effects of omeprazole on mechanosensitivity in humans using the barostat test. Omeprazole is a proton pump inhibitor that strongly decreases acid secretion. The data suggest that suppression of acid secretion may decrease mechanosensitivity of the proximal stomach as well as dyspeptic symptoms. Although the precise mechanisms are undetermined, the present study demonstrated that omeprazole decreases mechanosensitivity to mild gastric distension. These studies used the gastric barostat test in which a plastic bag with a double lumen polyvinyl tube was introduced into the stomach under fluorography. The tube was connected to a barostat device, which is a computer-controlled pump. Isobaric distensions were performed in stepwise increments. This method is the gold standard for evaluating gastric perception. This is a good descriptive study in which authors evaluate the effects of omeprazole on gastric mechanosensitivity in humans. The results are interesting and suggest that omeprazole decreases mechanosensitivity to mild gastric distension.

REFERENCES
1. Tack J, Talley NJ, Camilleri M, Holtmann G, Hu P, Malage-lada JR, Stanghellini V. Functional gastroduodenal disorders. Gastroenterology 2006; 130: 1466-1479
2. Talley NJ, Choung RS. Whither dyspepsia? A historical perspective of functional dyspepsia, and concepts of pathogenesis and therapy in 2009. J Gastroenterol Hepatol 2009; 24 Suppl 3: S20-S28
3. Mimidis K, Tack J. Pathogenesis of dyspepsia. Dig Dis 2008; 26: 194-202
4. Oostmanakakis P, Tack J. Dyspepsia: organic versus functional. J Clin Gastroenterol 2012; 46: 175-190
5. Lee KJ, Vos R, Janssens J, Tack J. Influence of duodenal acidification on the sensorimotor function of the proximal stomach in humans. Am J Physiol Gastrointest Liver Physiol 2004; 286: G279-G284
6. Veldhuyzen van Zanten SJ, Chiba N, Armstrong D, Barkun A, Thomson A, Smyth S, Escobedo S, Lee J, Sinclair P. A randomized trial comparing omeprazole, ranitidine, cisapride, or placebo in helicobacter pylori negative, primary care patients with dyspepsia: the CADET-HN Study. Am J Gastroenterol 2005; 100: 1477-1488
7. Talley NJ, Meineche-Schmidt V, Paré P, Duckworth M, Räsänen P, Pap A, Kordecki H, Schmid V. Efficacy of omeprazole in functional dyspepsia: double-blind, randomized, placebo-controlled trials (the Bond and Opera studies). Aliment Pharmacol Ther 1998; 12: 1055-1065
8. Tack J, Piessevaux H, Couillie B, Caenepeel P, Janssens J. Role of impaired gastric accommodation to a meal in functional dyspepsia. Gastroenterology 1998; 115: 1346-1352
9. Tack J, Caenepeel P, Piessevaux H, Cuomo R, Janssens J. Assessment of meal induced gastric accommodation by a satiety drinking test in health and in severe functional dyspepsia. Gut 2003; 52: 1271-1277
10. Boeckxstaens GE, Hirsch DP, van den Elzen BD, Heisterkamp SH, Tytgat GN. Impaired drinking capacity in patients with functional dyspepsia: relationship with proximal stomach function. Gastroenterology 2001; 121: 1054-1063
11. Tutuian R, Vos R, Karamanolis G, Tack J. An audit of technical pitfalls of gastric barostat testing in dyspepsia. Neurogastroenterol Motil 2008; 20: 113-118
Iida A et al. Omeprazole decreases gastric perception

12 Iida A, Konagaya T, Kaneko H, Funaki Y, Kanazawa T, Tokudome K, Hiiikata Y, Masui R, Ogawara N, Sasaki M, Yoneda M, Kasugai K. Usefulness of a slow nutrient drinking test for evaluating gastric perception and accommodation. *Digestion* 2011; 84: 253-260

13 Röhss K, Lind T, Wilder-Smith C. Esomeprazole 40 mg provides more effective intragastric acid control than lanosoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg and rabeprazole 20 mg in patients with gastro-oesophageal reflux symptoms. *Eur J Clin Pharmacol* 2004; 60: 531-539

14 Mearin F, Cucala M, Azpiroz F, Malagelada JR. The origin of symptoms on the brain-gut axis in functional dyspepsia. *Gastroenterology* 1991; 101: 999-1006

15 Tack J. Biscopps R, Sarnelli G. Pathophysiology and treatment of functional dyspepsia. *Gastroenterology* 2004; 127: 1239-1255

16 van Boxel OS, ter Linde JJ, Sieresea PD, Smout AJ. Role of chemical stimulation of the duodenum in dyspeptic symptom generation. *Am J Gastroenterol* 2010; 105: 803-811; quiz 802, 812

17 Miwa H, Nakajima K, Yamaguchi K, Fujimoto K, Veldhuizen VAN Zanten SJ, Kinoshita Y, Adachi K, Kusunoki H, Haruma K. Generation of dyspeptic symptoms by direct acid infusion into the stomach of healthy Japanese subjects. *Aliment Pharmacol Ther* 2007; 26: 257-264

18 Coffin B, Chollet R, Flourié B, Lemann M, Franchisseur C, Rambaud JC, Jian R. Intraluminal modulation of gastric sensitivity to distension: effects of hydrochloric acid and meal. *Am J Physiol Gastrointest Liver Physiol* 2001; 280: G904-G909

19 van den Elzen BD, Tytgat GN, Boeckstaens GE. Gastric hypersensitivity induced by oesophageal acid infusion in healthy volunteers. *Neurogastroenterol Motil* 2009; 21: 160-169

20 Simrén M, Vos R, Janssens J, Tack J. Acid infusion enhances duodenal mechanosensitivity in healthy subjects. *Am J Physiol Gastrointest Liver Physiol* 2003; 285: G309-G315

21 Ishii M, Kusunoki H, Manabe N, Kamada T, Sato M, Imamura H, Shiotani A, Hata J, Haruma K. Duodenal hypersensitivity to acid in patients with functional dyspepsia—pathogenesis and evaluation. *J Smooth Muscle Res* 2010; 46: 1-8

22 Jones RC, Xu L, Gebhart GF. The mechanosensitivity of mouse colon afferent fibers and their sensitization by inflammatory mediators require transient receptor potential vanilloid 1 and acid-sensing ion channel 3. *J Neurosci* 2005; 25: 10981-10989

23 Page AJ, Brierley SM, Martin CM, Price MP, Symonds E, Butler R, Wemmie JA, Blackshaw LA. Different contributions of ASIC channels 1a, 2, and 3 in gastrointestinal mechanosensory function. *Gut* 2005; 54: 1408-1415

24 Holzer P. Acid sensing by visceral afferent neurones. *Acta Physiol (Oxf)* 2011; 201: 63-75

25 Mearin F, Perez-Oliveras M, Perelló A, Vinyet J, Ibañez A, Coderch J, Perona M. Dyspepsia and irritable bowel syndrome after a Salmonella gastroenteritis outbreak: one-year follow-up cohort study. *Gastroenterology* 2005; 129: 98-104

26 La JH, Kim TW, Sung TS, Kang JW, Kim HJ, Yang IS. Visceral hypersensitivity and altered colonic motility after subsidence of inflammation in a rat model of colitis. *World J Gastroenterol* 2003; 9: 2791-2795

27 Dizdar V, Gilja OH, Hausken T. Increased visceral sensitivity in Giardia-induced postinfectious irritable bowel syndrome and functional dyspepsia. Effect of the 5HT3-antagonist ondansetron. *Neurogastroenterol Motil* 2007; 19: 977-982

28 Kedika RR, Souza RF, Spechler SJ. Potential anti-inflammatory effects of proton pump inhibitors: a review and discussion of the clinical implications. *Dig Dis Sci* 2009; 54: 2312-2317

S-Editor Gou SX  L-Editor A  E-Editor Li JY