Effects of Erythromycin on Plasma Gastrin, Somatostatin, and Motilin Levels in Healthy Volunteers and Postoperative Cancer Patients

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Erythromycin, an antibiotic agent, is known to be a motilin receptor agonist. Motilin is a peptide hormone that regulates gastric motility. One of the gastrointestinal motility regulatory factors has been assumed to be the induction of changes in the levels of peptides (gastrin, somatostatin and motilin) in plasma. We have elucidated the effects of erythromycin by examining changes in the plasma levels of gastrointestinal peptides. In this study, we investigated the effects of erythromycin on the plasma levels of gastrointestinal peptides (somatostatin, motilin, and gastrin) in healthy volunteers and patients with delayed gastric emptying (DGE). After a single oral administration, erythromycin caused a significant increase in plasma gastrin-like immunoreactive substance (IS) levels at 60 min. But the agent did not alter the levels of somatostatin-IS and motilin-IS. DGE is the most frequent postoperative complication after pylorus-preserving pancreateoduodenectomy. Motilin is assumed to be one important factor that influences DGE. We also examined the effects of erythromycin on the plasma motilin-IS levels of postoperative patients. The plasma motilin-IS levels were increased after 1 week of oral administration of erythromycin compared with preadministration. These results suggest that the pharmacologic effects of erythromycin in promoting gastric emptying are closely related to changes in plasma motilin-IS levels.

Key words erythromycin; motilin; delayed gastric emptying; pylorus-preserving pancreateoduodenectomy

Since erythromycin was introduced into clinical practice more than 45 years ago, serious adverse reactions to this drug have been surprisingly few. Adverse effects on the gastrointestinal tract are by far the most common side effects caused by erythromycin.1) Cramping, diarrhea, nausea, and occasional vomiting are the most common manifestations of those adverse effects. These effects tend to be dose related and occur with both oral and intravenous administration.2) Because of these adverse effects of erythromycin, clinical studies have been conducted to determine its effect on gastric emptying disorders. Studies have also analyzed the mechanism of erythromycin’s gastrokinetic activity.3)

One of the gastrointestinal motility regulatory factors has been assumed to be the induction of changes in the levels of peptides (gastrin, somatostatin, and motilin) in plasma. In recent years, some prokinetic medicines have been elucidated pharmacologically from the viewpoint of gut-regulated hormone levels. Among the medicines, Itoh et al. reported that cisapride, a dopamine D 2 receptor antagonist and nonselective serotonin 5-HT 4 agonist, raised motilin and gastrin levels.4) and mosapride, a selective serotonin 5-HT 4 receptor agonist, raised motilin and gastrin levels.5) Gastrin stimulates gastric acid secretion involving G cells and is associated with a mechanism of gastrointestinal motility involving the cholinergic nervous system.6) Somatostatin inhibits the secretion of other hormones, including gastrin, insulin, and motilin.7) In the gastrointestinal tract, gastric acid and pepsin secretion, and gastric emptying are inhibited by somatostatin.8) In the interdigestive state somatostatin induces phase-3 activities,9) and in the digestive state it inhibits gastric emptying10) and slows gastrointestinal transit.11) Motilin has a powerful fundic pouch motor-stimulating activity.12) It plays an important physiologic role in intestinal contractility and is one of the most important factors controlling the regular occurrence of phase-3 contractions of the migrating motor complex (MMC).13) Motilin participates in regulating gastrointestinal motility with somatostatin and stimulates gastric emptying and postprandial gastric contraction.

Erythromycin and related 14-member macrolide compounds act as motilin agonists by binding to motilin receptors and initiating phase-3 activity of the interdigestive MMC.14,15) Pylorus-preserving pancreateoduodenectomy (PPPD) has become accepted as a safe, appropriate operation in selected patients with malignant and benign disease of the pancreas and periampullary region.16) Delayed gastric emptying (DGE) is a leading cause of complications after PPPD, occurring in up to 50% of patients.17) The pathogenesis of DGE is thought to be gastric atony in response to resection of the duodenal pacemaker18) or reduction in circulating motilin levels.19) A prospective, randomized, placebo-controlled, double-blind study showed that erythromycin significantly accelerates gastric emptying after pancreateoduodenectomy and reduces the incidence of DGE.20) Although the clinical usefulness of erythromycin for DGE is well known, the relationship between erythromycin and motilin has not been investigated in humans.

The purpose of this study was to examine the effects of erythromycin on plasma levels of gastrointestinal peptides [gastrin-, somatostatin-, and motilin-like immunoreactive substance (IS)] in healthy volunteers and patients.

MATERIALS AND METHODS

Materials Erythromycin ethylsuccinate (Erythrocin; Dainippon Pharmaceutical Co. Ltd., Osaka, Japan) was used. Lactose (Merck Hoesi Co., Ltd., Osaka, Japan) was used as a placebo. Synthetic human gastrin I, somatostatin and motilin were purchased from the Peptide Institute, Inc. (Osaka, Japan). Fragment gastrin I (2—17) was purchased from Sigma (St. Louis, MO, U.S.A.). Antiserum to gastrin (A600/R1B) was purchased from Peninsula Laboratories (San Carlos, CA, U.S.A.), and motilin (Y121) from Yanaihara Institute (Shizuoka, Japan). All other reagents were of analytical purity.
reagent grade from commercial sources.  

Volunteers Five healthy male volunteers, aged 25—30 years (median 27 years), weighing 55—68 kg (median 63 kg) and 6 patients (4 men and 2 women), aged 55—74 years, weighing 43—75 kg, participated in this study. Each received information on the scientific purpose of the study, which was approved by the Ethics Committee of Oita Medical University, and subsequently gave informed consent. No healthy volunteer received any medication for 1 month preceding the study. The patients, who had cancer, complained of the DGE after surgery (Table 1).

Study Schedules Erythromycin 1200 mg or placebo was administered orally with 100 ml of water. The dose of erythromycin in this study was the maximum daily dose used in clinical therapy. Venous blood samples (10 ml) were taken from a forearm vein before and at 20, 40, 60, 90, 120, 180, and 240 min after administration of the drug. The study was carried out from 14:00 to 18:00. On the first day, each patient received placebo orally with 100 ml of water. From the next day, erythromycin was administered for 1 week. The dose of 400 mg (high-dose therapy, patients A, B, C) or 200 mg (low-dose therapy, patient D, E, F) of erythromycin was given three times daily. Blood samples were taken before and at 45 and 90 min after administration of the drug or placebo. The study was carried out before lunch (from 12:00 to 13:30) (patients A, B, E, F) or 2 h after lunch (from 14:00 to 15:30) (patients C, D) to avoid the effects of meals.

Preparation of Plasma Extracts The blood samples were placed in chilled tubes containing 500 kallikrein inhibitor units/ml of aprotinin and 1.2 mg/ml of EDTA. After centrifugation, plasma samples were diluted with 4% acetic buffer (pH 4.0), and loaded onto C18 reverse-phase cartridges (Sep-Pak C18; Millipore Corp., Milford, MA, U.S.A.). After washing with 4% acetic buffer, peptides were eluted with 70% acetonitrile in 0.5% acetate buffer (pH 4.0). Eluates were concentrated by spin-vacuum evaporation, lyophilized, and stored at −40 °C until use. The recovery of plasma somatostatin-, motilin-, and gastrin-IS were >90% with this extraction procedure (data not shown).

Enzyme Immunoassays for Somatostatin-, Motilin-, and Gastrin-IS Peptide levels in plasma were measured using a highly sensitive enzyme immunoassay for somatostatin, gastrin and motilin as previously described. The assay was performed using a delayed-addition method. Separation of bound and free antigen was performed on anti-rabbit IgG (55641, ICN Pharmaceuticals, Inc., Ohio, U.S.A.)-coated immunoplates (Nunc-Immuno Module Maxisorp F8, InterMed, Denmark). Human somatostatin, gastrin I (2—17) and motilin were conjugated with β-galactosidase using N-[(ε-maleimido-caproyloxy)-succimide according to the methods of Kitagawa et al.24) The enzyme immunoassays for somatostatin-, motilin-, and gastrin-IS were specific and highly sensitive to detection limits of 0.10, 0.04, and 0.80 fmol/well, respectively.

Statistical Analysis Results in the healthy volunteers are expressed as mean ± S.D. Comparison of mean values was performed using repeated-measure one-way analysis of variance and the paired t-test. The values in the patients were analyzed using the Wilcoxon signed-rank test for paired samples. A p-value of less than 0.05 indicated statistical significance.

RESULTS AND DISCUSSION

Erythromycin caused a significant increase in plasma gastrin-IS levels at 60 min (40.4 ± 8.2 pg/ml) compared with placebo (30.2 ± 8.4 pg/ml) (Fig. 1a). Erythromycin did not alter the level of somatostatin- and motilin-IS in healthy volunteers (Figs. 1b, c).

Although erythromycin did not alter the plasma levels of gastrin- and somatostatin-IS in patients (Figs. 2a, b), the medicine caused a significant increase in motilin-IS after 1-week administration of the agent, compared with before administration (Fig. 2c). Furthermore, although the plasma motilin-IS levels in the control group were not altered during 90 min, that in the erythromycin-treated group was significantly increased from 0 to 45 min and from 45 to 90 min.

In this study, the ages differed greatly between the healthy volunteers and patients. Furthermore, the patients had cancer and had undergone surgery. Therefore it is possible that the plasma peptide levels were influenced by age, disease, or surgery. However, the plasma peptide levels before medication were not significantly different between the healthy volunteers and patients. We consider that, in this study, the influence of age, etc. on plasma peptide levels was slight.

In Fig. 1a, the temporary elevation in gastrin-IS levels in participants receiving placebo (20 min) might have been caused by the stimulation of gastric mucosal G cells. Erythromycin significantly increased gastrin-IS levels at 60 min compared with the response of the placebo groups. Therefore we assumed that the erythromycin groups showed two-phase (20-min, nonspecific, which was caused by the oral administration of any substances; 60-min, erythromycin-specific) increases in this study. The highest plasma erythromycin levels after oral administration of the agent were seen at 45 min. The increase in gastrin-IS levels was thought to be closely related to plasma erythromycin concentration. It was reported that clar-
ithromycin, which is a structural analogue of erythromycin, influenced circulating gastrin levels in human subjects. Further study may yield more interesting information on the effects of erythromycin on gastric acid secretion or gastric motility related to gastrin.

Erythromycin is known to act as motilin agonist and to accelerate gastric emptying in healthy volunteers. However, erythromycin did not influence plasma somatostatin- and motilin-IS levels in healthy volunteers. A single administration may not influence plasma somatostatin and motilin levels, or erythromycin may accelerate gastric emptying via a mechanism other than the motilin-related pathway.

Erythromycin is often used to treat DGE complications after PPPD. In this study, the 6 patients complained of poor appetite, nausea, or vomiting, and endoscopic or X-ray examination revealed that they had DGE. The dose of erythromycin used was the daily maximum dose (1200 mg). However, lower-dose administration was reported also to be effective in treating DGE. Therefore the half dose of erythromycin 600 mg was administered. The result was not significantly different between high- and low-dose therapies. The period of administration was limited to 1 week to prevent the occurrence of resistant bacteria because erythromycin is an antibiotic. The study schedule was different from in the healthy volunteers and patients because we did not want to burden postoperative patients with the stress of repetitive blood sampling.

Administration of erythromycin resulted in an improvement of DGE within a few days. The plasma motilin-IS levels were significantly increased after administration of erythromycin compared with the levels before administration. The improvement of DGE was thought to be closely related to the increase in motilin-IS levels. Single administration of erythromycin did not influence plasma motilin-IS levels in healthy volunteers, but the plasma motilin-IS levels in the patients have been increased significantly. The difference may have been due to the administration period. There have been several reports on the period of administration. Three-day administration of erythromycin resulted in a recurrence of DGE. There was also a case report that 1-month administration of erythromycin improved DGE. The plasma motilin-IS level may be one indicator of the effects of erythromycin.

The pharmacologic mechanism by which erythromycin improves DGE may be hypothesized as follows: erythromycin acts as motilin receptor agonist and accelerates gastric emptying without stimulation of motilin secretion. Therefore single administration did not cause an increase in

Fig. 1. Effects of Erythromycin (●) or Placebo (○) on Plasma Gastrin- (a), Somatostatin- (b), and Motilin-IS (c) Levels in Healthy Volunteers

Each value represents the mean±S.D., n=5. *p<0.05, significantly different compared with placebo.

Fig. 2. Levels of Plasma Gastrin- (a), Somatostatin- (b), and Motilin-IS (c) before and after 1-Week Administration of Erythromycin

Patients A (●), B (▲), C (■), D (○), E (△), and F (□). *p<0.05 and **p<0.01 significantly different compared with placebo.
motilin-IS levels. Repeated administration becomes a cue for motilin secretion and normalization. The motilin-IS levels in erythromycin-treated patients were increased by the stimulation of oral administration.

Erythromycin is an antibiotic, and antibiotics are not used to treat DGE. In our hospital, it was finally used when DGE did not improve with other prokinetics. Further study is needed to compare the effects of erythromycin with those of standard prokinetics such as metoclopramide, domperidone, and mosapride.

We could not compare the present results, because the study schedule was different for the healthy volunteers and patient. In summary, although erythromycin did not alter plasma motilin-IS levels, repeated doing for 1 week resulted in a significant increase in plasma motilin-IS levels. We hypothesize that the pharmacologic effects of erythromycin may be closely related to changes in plasma motilin-IS levels.

REFERENCES