Causes of, and therapeutic approaches for, proton pump inhibitor-resistant gastroesophageal reflux disease in Asia

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Abstract: Proton pump inhibitors (PPIs) are the most widely used drugs for treatment of gastroesophageal reflux disease. However, approximately 20% of patients with reflux esophagitis and 40% of those with nonerosive reflux diseases complain of troublesome symptoms, even during treatment with PPIs. In patients with reflux esophagitis, dose escalation and co-administration with a histamine H₂-receptor antagonist are potential approaches, since the major cause of PPI resistance is incomplete suppression of gastric acid secretion. On the other hand, for patients with nonerosive reflux disease, switching from PPIs to pain modulators is often necessary for improvement of symptoms, since 25% of patients with nonerosive reflux disease have symptoms not caused by gastroesophageal acid reflux. Therapeutic approaches for PPI-resistant patients with reflux esophagitis and nonerosive reflux diseases are considered according to pathogenesis.

Keywords: proton pump inhibitor, gastric acid secretion, gastroesophageal reflux disease, reflux esophagitis, nonerosive reflux disease, heartburn

Introduction

Proton pump inhibitors (PPIs) are the most effective drug treatment for gastroesophageal reflux disease (GERD) and are widely used in both Western and Asian countries. Gastric acid secretion in the Japanese population is lower than in the Western population [Kinoshita *et al.* 1997]; therefore, the expectation has been that PPIs would relieve GERD symptoms and esophageal mucosal lesions in almost all Japanese patients with GERD. In Asian countries, however, a significant number of patients still complain of heartburn during PPI therapy. In this review, we will describe the current medical therapy for GERD in Asian countries and then discuss the possible causes of, and therapeutic approaches for, PPI-resistant GERD.

Current medical therapy for GERD

GERD is caused by the reflux of gastric contents into the esophagus. Affected patients are troubled by complications such as esophageal ulcers, bleeding, perforation and stricture, as well as

other unpleasant symptoms. The prevalence of GERD has been steadily increasing, even in Asian countries [Wong and Kinoshita, 2006] and approximately 20% of individuals who received an annual medical check in Japan were diagnosed with GERD [Mishima *et al.* 2005]. Although the pathogenesis of GERD is not fully understood, an impaired reflux barrier between the esophagus and stomach, and decreased clearance of the esophagus, are believed to be the major causes. Thus, pharmacological or surgical reconstruction of the reflux barrier as well as pharmacological acceleration of esophageal clearance are theoretically ideal procedures for treatment of patients with GERD. However, these pharmacological effects are difficult to attain, since there is no drug available that is adequate for these purposes. Although some prokinetic drugs have been reported to prevent gastroesophageal reflux [Ruth *et al.* 1998, 2003] and facilitate esophageal clearance of refluxed gastric contents [Cho *et al.* 2006], their therapeutic potential for treatment of GERD is known to be limited. Therefore, drugs that decrease gastric

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acidity have been used as first-line treatment options for GERD to decrease the corrosive and irritating effects of the refluxant.

Three kinds of drugs that decrease gastric acidity are widely used, among which acid-neutralizing agents such as aluminum hydroxide are able to increase intragastric pH quickly after being taken, though the duration of their effect is limited to as short as 1 h, based on intragastric pH monitoring data. Therefore, this type of drug is now considered to be a rescue drug and used only for postprandial heartburn.

Histamine H₂-receptor antagonists (H₂RAs) are potent drugs for inhibiting gastric acid secretion, and can dramatically decrease the incidence of gastroduodenal ulcers and surgery for patients with peptic ulcers. However, H₂RAs have three important limitations when given for treatment of patients with GERD. First, their acid-suppressing effects are limited during the daytime postprandial period in comparison with the nocturnal period [Komazawa *et al.* 2003] and gastroesophageal reflux in the majority of patients occurs during the daytime postprandial period [Adachi *et al.* 2001]. Therefore, the diurnal profile of the acid-suppressing effects of H₂RAs does not fit with the necessary characteristics of drugs used for patients with daytime-predominant gastroesophageal reflux. Second, the acid-suppressing effects of H₂RAs rapidly wane within 2 weeks during continuous daily administration [Komazawa *et al.* 2003]. This rapid lessening of effect (i.e. tachyphylaxis) has been found with all types of H₂RAs. Thus, these drugs are generally used to inhibit acid secretion for a short period, especially in patients not infected by *Helicobacter pylori* [Fujisawa *et al.* 2004]. Acid inhibitors are effective for complications and unpleasant symptoms associated with GERD; however, they do not treat pathophysiological abnormalities that cause pathological gastroesophageal reflux. Therefore, stopping administration of an H₂RA is often accompanied by recurrence of GERD and long-term administration of acid-suppressing drugs is often necessary as maintenance treatment in these patients, though H₂RAs are not appropriate for long-term control of acid secretion because of tachyphylaxis. Third, the dose of H₂RAs must be adjusted based on renal function, since they are mainly removed via the kidneys. In Japan, elderly females have a higher risk for development of GERD and often complain of reflux symptoms

[Hirakawa *et al.* 1999]. In addition, elderly individuals have a higher risk of impaired renal function and over 30% are reported to have a decreased glomerular filtration rate. When administering H₂RAs for treatment of elderly patients with GERD, dose adjustment based on renal function is a troublesome additional step.

PPIs are the most potent inhibitors of gastric acid secretion and have several advantages over other types of acid inhibitors when used for treatment of GERD. The daytime postprandial acid inhibitory effect of PPIs is potent enough to prevent postprandial acid reflux in the esophagus [Katsube *et al.* 2000] and they do not lose their potent antisecretory effects during long-term continuous administration. PPIs are metabolized mainly in the liver and their action is not influenced by renal function. Therefore, dose adjustment is not necessary, even in elderly patients with renal insufficiency. For these reasons, PPIs are now considered to be most suitable for treatment of GERD, and are widely used as first-line drugs for treatment of nonerosive reflux disease (NERD) and reflux esophagitis.

When used for treatment of reflux esophagitis, PPIs cure 80% of reflux symptoms, such as heartburn and acid regurgitation, reported by patients [Miwa *et al.* 2007]. In addition, they are able to heal over 90% of mucosal breaks detected by endoscopy in patients with reflux esophagitis [Soga *et al.* 1999]. Nevertheless, 20% of patients continue to complain of troublesome reflux symptoms and 10% have mucosal breaks during continuous PPI administration. When used for treatment of NERD, the therapeutic effects of PPIs are limited and only 50–60% of patients with NERD become successfully free from reflux symptoms with their administration [Miwa *et al.* 2007; Kinoshita *et al.* 2006].

Causes of, and therapeutic approaches for, PPI-resistant reflux esophagitis

Inappropriate timing of PPI administration

For activation of an administered PPI in the secretory canaliculi of gastric parietal cells, active acid secretion and acidic milieu in the secretory canaliculi are necessary. The plasma concentration of a PPI usually reaches its maximum level at approximately 2h after oral administration. To maximally stimulate gastric acid secretion at the point when plasma PPI concentration reaches its peak,

it is considered best to administer the PPI at 0.5–1.0 h before a meal, usually before breakfast [Gunaratnam *et al.* 2006]. However, clinical and physiological evidence to support that notion is scarce, though a PPI administered before meals was reported to inhibit acid secretion more effectively than a PPI administered during a period of fasting [Hatlebakk *et al.* 2000]. We previously compared the acid-inhibiting effects of PPIs administered before or after meals using 24-h intragastric pH monitoring [Miki *et al.* 2006]. Interestingly, the acid-suppressing effects of PPIs were not influenced by the different timing of administration, even when taken after meals, as they inhibited acid secretion with a potency similar to that observed with premeal PPI administration. While it is generally recommended that PPIs should be administered before meals, the data to support this practice are limited and a long-term clinical study would be necessary to confirm this.

Polymorphism of PPI degrading enzyme, CYP2C19

Omeprazole, lansoprazole and pantoprazole are mainly catabolized and inactivated by the liver enzyme, CYP2C19. Therefore, when the activity of that enzyme is reduced, the plasma concentration of an administered PPI becomes greater and the acid-suppressing effect stronger [Adachi *et al.* 2000; Furuta *et al.* 1999]. Since the major catabolic pathways of rabeprazole and esomeprazole are not dependent on this enzyme, their effects are not greatly influenced by CYP2C19 enzyme activity. In Western countries, the ratio of poor metabolizers is reported to range from 1% to 2%, thus the Western population does not have a large influence on PPI treatment for GERD. In an Asian population, approximately 20% of tested individuals had limited CYP2C19 enzyme activity and were considered to be poor metabolizers of PPIs [Yamada *et al.* 2001]. In such cases, the acid-suppressing effects of PPIs are augmented and their therapeutic potential for treatment of GERD is reported to be enhanced [Kawamura *et al.* 2003]. Therefore, a genetic polymorphism of CYP2C19 is not a causative mechanism of PPI-resistant reflux esophagitis.

Nocturnal gastroesophageal acid reflux

Although the majority of patients with reflux esophagitis have daytime postprandial gastroesophageal reflux, the diurnal pattern of reflux differs between different grades of reflux esophagitis (A, B, C and D), which are categorized based on the size and form of the esophageal mucosal

breaks [Kusano *et al.* 1999; Lundell *et al.* 1999]. Patients with short longitudinal mucosal breaks (reflux esophagitis grade A) have predominant daytime postprandial reflux [Adachi *et al.* 2001], while those with higher grades (C and D) have longitudinal mucosal breaks as well as transverse lesions connecting them, and experience nocturnal predominant gastroesophageal acid reflux [Adachi *et al.* 2001]. Robertson *et al.* [1987] also reported a similar observation. Thus, daytime postprandial reflux caused by transient lower esophageal sphincter relaxation is the type of reflux observed mainly in cases with lower grade reflux esophagitis. On the other hand, nocturnal reflux caused by decreased resting lower esophageal sphincter pressure is observed mainly in patients with higher-grade reflux esophagitis. When PPIs are administered to patients with lower-grade reflux esophagitis, mucosal breaks in nearly all cases can be easily cured, as compared to patients with higher grade esophagitis such as grade C or D, of whom only 70–80% can be healed [Labenz *et al.* 2005; Castell *et al.* 2002]. The different therapeutic effects of PPIs on different grades of esophagitis may be caused by the different types of gastroesophageal reflux patterns, as described above.

When PPIs are administered to patients with *H. pylori* infection, intragastric pH will usually rise to a neutral level for the entire day [Katsube *et al.* 2000]. Therefore, in those cases PPIs are potent enough for treatment of any type of acid-related disease, including GERD. In the absence of *H. pylori*, PPIs are not potent enough to raise nocturnal intragastric pH, though they can increase intragastric pH to neutral during the postprandial daytime period [Adachi *et al.* 2003; Katsube *et al.* 2000]. Long-lasting (usually more than 1 h) nocturnal intragastric acidification even during PPI administration is called ‘nocturnal gastric acid breakthrough’ and often observed in cases not infected by *H. pylori*. Furthermore, more than 70% of patients with high-grade reflux esophagitis were reported to be not infected [Fujishiro *et al.* 2001; Shirota *et al.* 1999]. Therefore, intragastric pH control during the nocturnal period by administration of standard doses of PPIs is often difficult in these patients. PPI failure observed during treatment of high-grade reflux esophagitis may be caused by the limited acid-suppressing effects of PPIs, especially during the nocturnal period when patients with high-grade esophagitis frequently experience gastroesophageal acid reflux.

For the treatment of PPI-resistant patients with high-grade reflux esophagitis, medical and surgical approaches are possible. One of the best medical approaches is administration of double-dose PPI and is usually recommended in Western countries [Fass *et al.* 2005]. In Japan, double-dose PPI administration is strictly regulated by the government regulating committee. Therefore, dividing the standard PPI dose into two (morning and evening doses) may be a practical option rather than a single undivided dose. We investigated whether such an approach can elevate nocturnal intragastric pH using a 24 h pH monitoring study and found that splitting PPI doses elevated nocturnal intragastric pH without decreasing PPI-induced daytime pH elevation [Adachi *et al.* 2003]. Therefore, twice-daily administration of a PPI, even if the total dose equals the standard one, is considered to be a useful option for PPI-resistant cases.

The addition of an H2RA to the standard single morning dose of PPI is another option. H2RAs are effective for inhibiting gastric acid secretion during the nocturnal period and remarkably raise nocturnal intragastric pH, even in cases not infected with *H. pylori* [Fujisawa *et al.* 2004]. The acid-secretion-suppressing effects of H2RAs show a tolerance phenomenon, thus after 2 weeks of administration the effects fade remarkably in uninfected cases. In *H. pylori*-infected cases, H2RAs show little tolerance phenomenon and the acid-suppressing effects last longer [Fujisawa *et al.* 2004]. Approximately 70% of patients with high-grade reflux esophagitis are reported to be negative for *H. pylori* infection, even in Japan where the infection rate is higher than in Western countries. Therefore, the supplementary acid-suppressing effect observed by adding an H2RA to a PPI fades within a short period of time, even if the supplementary administration of H2RA is employed at bedtime [Adachi *et al.* 2003]. We administered supplementary bedtime H2RA to five patients with PPI-resistant high-grade reflux esophagitis [Adachi *et al.* 2004] and found that esophagitis was cured and reflux symptoms disappeared in four patients, which continued for more than 1 year. From these observations, inhibition of acid secretion by the combined use of PPIs and H2RAs, even if their combined effects fade in a short period of time, and it may be worthwhile to evaluate this as a possible treatment for PPI-resistant cases in a large randomized controlled study.

Surgery is another option for PPI-resistant patients. According to previous studies, the healing effects of surgery for reflux esophagitis are compatible with those of medical treatment [Lundell *et al.* 2000], however, data regarding long-term effects are scant [Vakil, 2007; Vakil *et al.* 2003]. Although surgery for reflux esophagitis is often performed in the US, it is not widely accepted in Japan, partly because of the lack of long-term data and the possibility of procedure-related complications including dysphagia, as well as the limited number of well-trained surgeons who have adequate experience with this type of surgery.

Drugs that may aggravate esophagitis

Several different drugs are known to trigger and/or aggravate gastroesophageal acid reflux, and may prevent healing. The evidence concerning the role of these drugs for the development of PPI-resistant reflux esophagitis is still lacking. Theophylline, used for the control of bronchial asthma, and calcium antagonists, given for control of hypertension and ischemic heart disease, may suppress the functions of the lower esophageal sphincter and peristaltic esophageal contraction with delayed acid clearance, though evidence suggesting their side-effects have not been completely confirmed [Ekström and Tibbling, 1988; Vandenplas *et al.* 1986; Richter *et al.* 1985]. Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs), which are widely and increasingly used for the prevention of cerebrovascular and coronary heart disease as well as control of somatic pain, are another group of drugs that may delay esophageal healing [Sontag *et al.* 2006; Kim *et al.* 1999]. Aspirin/NSAIDs are known to decrease the production of prostaglandins in the esophageal mucosa, which may decrease mucosal protection resulting in esophageal mucosa vulnerable to acidic refluxant. In addition, these drugs are reported to increase the production of gastric acid and decrease intragastric pH [Kataoka *et al.* 2000; Savarino *et al.* 1998]. The combination of increased refluxant acidity and vulnerable esophageal mucosa may prevent complete healing of esophagitis, even during chronic PPI administration. In addition, patients with esophagitis who take aspirin/NSAIDs may have a higher risk of bleeding complications [Taha *et al.* 2006]. Bisphosphonates, used for the treatment of osteoporosis, are also known to cause esophagitis, if the drugs remain longer in the esophagus [de Groen *et al.* 1996]. Withdrawal of these drugs or switching to other

types may be necessary if the patient shows resistance to standard PPI treatment. If one of these medications cannot be safely changed to an alternative agent, double-dose PPI divided into two doses may be considered for treatment of standard PPI-resistant cases. The value of these therapeutic strategies should be tested in a controlled study in the future.

Causes of, and therapeutic approaches for, PPI-resistant NERD

NERD is defined by the presence of troublesome reflux-associated symptoms and absence of mucosal breaks shown by endoscopy, according to the Montreal definition and classification of gastroesophageal reflux disease [Vakil *et al.* 2006]. Patients are divided into three groups according to the results of intraesophageal pH monitoring. The first is composed of those with abnormally high levels of gastroesophageal acid reflux, with approximately half of the patients with NERD classified into this group. The second is a group of patients with normal physiological gastroesophageal acid reflux, which comprise about 25% of all NERD cases. Acid reflux observed in these patients is accompanied by reflux symptoms and the symptom index value (number of reflux associated symptoms/number of total symptoms $\times$ 100) should be over 50. The majority of reflux symptoms noted by patients in these first two groups are caused by the reflux of acidic gastric contents. Therefore, PPI administration to decrease intragastric acidity is expected to relieve their reflux symptoms, although it is known that NERD patients with only a mildly abnormal pH test generally demonstrate a lower response to PPI treatment. The third group consists of patients who have frequent reflux symptoms not accompanied by acidic gastroesophageal reflux. In these cases, reflux symptoms are not considered to be caused by reflux of acidic gastric contents, but rather nonacidic reflux or esophageal hypersensitivity, though the precise mechanisms involved with the induction of reflux symptoms are not clear. PPI administration, even at higher doses, does not relieve the symptoms of patients in this group. These cases comprise about 25% of all cases with NERD and are also called 'functional heartburn' [Hershovici and Zimmerman, 2008; Galmiche *et al.* 2006]. Since approximately one-fourth of all patients with NERD have symptoms not caused by acid, the therapeutic effects of acid-suppressing drugs are limited, even if potent

acid-inhibiting drugs including PPIs are used [Hongo *et al.* 2008; Miwa *et al.* 2007].

Acid hypersensitivity and inadequate PPI doses

As noted above, NERD is classified into three groups. In groups 1 and 2, esophageal reflux of acidic contents from the stomach is the causative factor that induces reflux symptoms such as heartburn and acid regurgitation. In patients with NERD, the time of acid exposure in the lower esophagus, usually 5 cm above the proximal end of the lower esophageal sphincter, is shorter than that in patients with endoscopically proven reflux esophagitis, though the intensity and frequency of reflux symptoms are similar between cases with NERD and those with reflux esophagitis. To explain the discrepancy between the severity of reflux symptoms and shorter acid contact time, many investigators have speculated that the esophageal mucosa of NERD patients has acid hypersensitivity, and several reports supporting this notion have been published [Emerenziani *et al.* 2008; Knowles and Aziz, 2008; Wu *et al.* 2007]. A dilated esophageal epithelial intercellular space and/or defective secondary peristalsis have been proposed as possible mechanisms related to acid hypersensitivity [Iwakiri *et al.* 2007; Tobey *et al.* 1996]. Thus, patients with NERD may have acid-sensitive esophagi that necessitates stronger inhibition of gastric acid secretion for relief of reflux symptoms. In these cases, weakly acidic reflux or nonacidic bile reflux during PPI treatment may irritate the sensitive esophagus and cause GERD symptoms.

PPIs in standard doses strongly inhibit gastric acid secretion, especially in cases with *H. pylori* infection. However, acid secretion of about 10% remains even during the administration of standard doses. Therefore, acidic and weak acidic reflux may remain in NERD cases, causing reflux symptoms in those with an acid-sensitive esophagus. In these cases, administration of a higher PPI dose may improve the symptoms of patients with standard-dose PPI-resistant NERD [Lind *et al.* 1997], though adequate evidence supporting the effectiveness of this approach has not been obtained. Other medical trials using subjects with PPI-resistant NERD have been performed, which showed that tricyclic antidepressants and selective serotonin receptor inhibitors (SSRIs) may relieve reflux symptoms by modulating esophageal acid sensitivity as pain modulators [Broekaert *et al.* 2006; Tack and Fass, 2004].

Nonacid reflux causing reflux symptoms

In NERD patients with symptoms caused by nonacid reflux, also called *functional heartburn*, acid is not responsible for the induction of reflux symptoms. Thus, drugs that decrease gastric acid secretion are not effective. These patients have been reported to have hypersensitivity to nonacidic fluid and/or gas reflux, and to complain of symptoms [Emerenziani *et al.* 2008]. Reflux inhibitors are possible therapeutic drugs for such patients. Although there are a number of reports suggesting the usefulness of cisapride, a prokinetic agent, it has been withdrawn from the market because of cardiac side-effects. At higher doses, mosapride, a selective serotonin receptor 4 agonist, has also been reported to facilitate esophageal clearance by stimulating esophageal motor functions [Cho *et al.* 2006; Ruth *et al.* 1998]. Therefore, mosapride and other prokinetic drugs may be administered as possible therapeutic drugs for patients with PPI-resistant functional heartburn.

Pain-modulating agents are a possible therapeutic option for patients with nonacid reflux. Citalopram, an SSRI, was recently reported to lower chemical and mechanical esophageal sensitivity in esophageal hypersensitivity [Broekaert *et al.* 2006]. Therefore the effectiveness of pain-modulating drugs including SSRIs and tricyclic antidepressants should be established for functional heartburn.

Mental stress aggravating reflux symptoms

Psychological distress tends to worsen GERD symptoms and quality of life before and even after PPI therapy [Nojkov *et al.* 2008]. Furthermore, sleep deprivation and auditory stress were reported to enhance unpleasant reflux symptoms [Fass *et al.* 2008; Schey *et al.* 2007]. Therefore, drugs that decrease anxiety and stress may be useful for PPI-resistant NERD, and a study to investigate the value of these types of drugs is necessary.

Summary

In summary, PPIs have potent acid-inhibiting effects, and can heal and relieve esophagitis and reflux symptoms in the majority of cases with GERD. Approximately 10% of patients with endoscopically proven reflux esophagitis show

resistance to PPI treatment, because of inadequate acid suppression and/or concomitantly administered aggravating agents. For these cases, dose escalation of the PPI and withdrawing administration of possible aggravating agents are the first approach that should be taken. If that fails, a pH monitoring study should be considered to clarify the pathogenesis. In addition, as many as 40% of patients with NERD have resistance to PPI administration. Since reflux symptoms in approximately 30% of patients with NERD are not caused by the reflux of acid but rather by nonacid reflux, monitoring of pH and impedance should be considered in the early stages of therapy. For high-dose PPI-resistant NERD, administration of pain modulating and/or prokinetic agents may be considered as a second-line treatment.

Conflict of interest statement

The authors declare that no financial or other conflict of interest exists in relation to the content of this article.

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