A Proton Pump Inhibitor, Lansoprazole, Ameliorates Asthma Symptoms in Asthmatic Patients with Gastroesophageal Reflux Disease

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SHIMIZU, Y., DOBASHI, K., KOBAYASHI, S., OHKI, I., TOKUSHIMA, M., KUSANO, M., KAWAMURA, O., SHIMOYAMA, Y., UTSUGI, M., SUNAGA, N., ISHIZUKA, T. and MORI, M. A Proton Pump Inhibitor, Lansoprazole, Ameliorates Asthma Symptoms in Asthmatic Patients with Gastroesophageal Reflux Disease. Tohoku J. Exp. Med., 2006, 209 (3), 181-189 —— Aspiration of acid to the airway causes airway inflammation, and acid stress to the airway caused by gastroesophageal reflux disease (GERD) has been known as a potential mechanism of deteriorated asthma symptoms. However, the efficacy of the acid suppressive drugs, H₂-receptor blockers (H₂ blocker) and proton pump inhibitors, on asthma symptoms and pulmonary functions remains controversial. We therefore designed the randomized prospective study to determine the efficacy of an H₂ blocker (roxatidine, 150 mg/day) and a proton pump inhibitor (lansoprazole, 30 mg/day) on asthma symptoms of 30 asthmatic patients with GERD. These patients were divided in the two groups (15 patients for each group) and treated with either roxatidine or lansoprazole. The diagnosis of GERD was established by the method of Los Angeles classification including mucosal minimum change of Grade M and questionnaire for the diagnosis of reflux disease (QUEST) score. The efficacy of acid suppressive drugs was evaluated by peak expiratory flow (PEF), asthma control questionnaire (ACQ) that evaluates the improvement of asthma symptoms, and forced expiratory volume in 1 second (FEV₁₀). Lansoprazole, but not roxatidine, significantly improved PEF and ACQ scores (p < 0.05) with the improved QUEST scores. However, these acid suppressive drugs did not change the pulmonary function of FEV₁₀ in asthmatic patients. In conclusion, treatment with a proton pump inhibitor, lansoprazole, appears to be useful in improvement of asthma symptoms in asthmatic patients with GERD. ——— asthma; gastroesophageal reflux disease; proton pump inhibitor; H₂-receptor blocker

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Potential mechanisms to explain the relationship between asthma and gastroesophageal reflux disease (GERD) include microaspiration of acid into the airway (Tuchman et al. 1984), vagal reflex response to acid aspiration (Altschuler 2001), neuroinflammatory reflex to acid stimuli-induced synergistic interactions between esophageal nociceptors and airway sensory nerves (Caning and Mazzone 2003), and airway pH deviation-induced inflammatory cell activation in the airway (Ricciardolo et al. 2004). These mechanisms imply that the elimination of acid stress from the airway would contribute to an improvement in patients with asthma. There have been many studies dealing with asthma outcome and medical anti-reflux therapy. Field and Sutherland (1998) reviewed the previously published data on medical anti-reflux therapy with H$_2$-receptor blockers (H$_2$ blockers), cimetidine (Goodall et al. 1981; Larrain et al. 1991) and ranitidine (Harper et al. 1987; Nagel et al. 1988; Ekstrom et al. 1989; Gustaffson et al. 1992), and with a proton pump inhibitor (PPI) omeprazole (Ford et al. 1994; Meier et al. 1994; Harding et al. 1996; Teichtahl et al. 1996), showing that asthma symptoms were improved. Kiljander (2003) suggested that, in the management of GERD-related asthma, PPIs other than omeprazole should be used at double the standard dose. A PPI, rabeprazole, was proven to inhibit gastric acid secretion (Hongo et al. 1998). Recently, rabeprazole at 20 mg b.i.d. (double the standard dose) was shown to improve the morning and evening peak expiratory flow rates (PEF) in asthmatic patients (Tsugeno et al. 2003). Lansoprazole, another PPI, has also been shown to be effective for the treatment of GERD (Chiba 1997; Malagelada 2004). Although Kiljander (2003) recommended that lansoprazole be given at double the standard dose (30 mg b.i.d.) in asthmatic patients, there have been no studies of the effect of roxatidine in asthmatic patients with GERD.

The present study was designed to determine the efficacy of an H$_2$ blocker (roxatidine, 150 mg/day) and a PPI (lansoprazole, 30 mg/day) on asthma symptoms and the pulmonary function in asthmatic patients with GERD. In this study, we first examined the presence of GERD in asthmatic patients on endoscopic examination using the Los Angeles classification (LA classification) (Armstrong et al. 1996) with the addition of Grade M (Hoshihara and Hashimoto 2000), defined as minimal change of the esophageal mucosa to observe acid exposure for esophageal mucosa precisely, and also presence of GERD was evaluated by questionnaire for the diagnosis of reflux disease (QUEST) (Carlsson et al. 1998). We then examined the changes in the QUEST scores to evaluate GERD symptoms, morning PEF and forced expiratory volume in 1 second ($FEV_1.0$) to evaluate asthma status objectively, and asthma symptoms using asthma control questionnaire (ACQ) (Juniper et al. 1999) in the two groups.

**METHODS AND STUDY DESIGN**

**Subjects**

The diagnosis of asthma was based on the American Thoracic Society’s definition of asthma (American Thoracic Society 1962). Asthmatic patients were excluded if they were pregnant or lactating, under 16 years of age, smokers, mentally incompetent, or had liver, kidney, or other severe diseases. Patients with a history of esophageal, gastric, or duodenal surgery were also excluded, as were patients with a history of drug-induced allergy and those being treated with an angiotensin-converting enzyme (ACE) inhibitor, a muscarine receptor antagonist or acid suppressive drugs. Asthma medications were given according to the levels of the severity defined by Global strategy for asthma treatment and prevention, Global initiative for asthma® (GINA) (National Institute of Health, National Heart, Lung, and Blood Institute 2003). The levels of asthma severity in GINA are described in the following section. Asthma medications were not changed during the study period.
Grading of asthma severity and the asthma treatment score

Asthma severity was graded using GINA. GINA classifies asthma status into 3 general levels, mild, moderate and severe, with the mild level being further divided into two levels. Briefly, level 1 is called the mild intermittent type with asthma symptoms appearing less than once a week, and the PEF is over 80% of predicted flow. Level 2 is called the mild continuous type with asthma symptoms appearing more than once a week, though not every day, and the PEF is over 80% of predicted flow. Level 3 represents the moderate continuous type with asthma symptoms appearing every day, and the PEF is from 60% to 80% of predicted flow. Level 4 represents the severe continuous type with asthma symptoms worsening despite asthma treatment, and the PEF is less than 60% of predicted flow. In present study, the changes in asthma symptoms were assessed using the ACQ (Juniper et al. 1999). The ACQ has been used in the previous studies (Vollmer et al. 1999; Rosenhall et al. 2003), and composes of 6 questions for patients and 1 question for the doctors, which is easy to answer. The ACQ has been proven to correlate with asthma control. Each question was about the frequency of woken by asthma during night, or morning, limitation of activities, shortness of breath, wheeze, puffs of short-acting bronchodilator and levels of FEV1.0. Patients answer the questions according to their symptoms levels 0 (never) – to 6 (very severe). FEV1.0 were graded 0 (> 95% predicted) to 6 (< 50% predicted). To evaluate airflow limitation, PEF was measured using a Mini Wright PEF meter (Health Scan Products Inc., Cedar Grove, NJ, USA) using the American Thoracic Society (ATS) scale. The patients measured PEF every morning. The two-week means of PEF before treatment and the two-week means before the end of the study (the seventh and eighth weeks) were used for evaluation. Pulmonary function of FEV1.0 was measured by CHESTAC~55V (CHEST MI, Tokyo).

Evaluation of GERD

The diagnosis of GERD was established by endoscopic examination using the LA classification (Armstrong et al. 1996) of Grade A to D with minimum change of Grade M and no apparent mucosal change of Grade N (Hoshihara and Hashimoto 2000). Grade M (minimal change) is defined by the presence of prominent erythema without clear demarcation or whitish cloudiness of the lower esophageal mucosa obscuring the longitudinal blood vessels. The LA classification defines the changes of a clearly esophageal mucosal break as an area of slough or erythema demarcated from adjacent normal-appearing mucosa. It has been reported that there is a large number of patients with GERD who are below Grade A, and are labeled as Grades N and M (Hoshihara et al. 2000). To observe acid exposure for esophageal mucosa precisely, we use the LA classification with grade M and N. In our randomized study, the LA classification was determined before starting H2 blocker or PPI treatment. Diagnosis of GERD was made by four endoscopists (Shimoyama et al. 2005). A QUEST score, which has been proven to be useful in the assessment of GERD, was used to assess GERD symptoms (Carlsson et al. 1998; Tsugeno et al. 2003). A QUEST score ≥ 4 was diagnostic of GERD.

Randomized study design

The design of the randomized study is shown in Table 1. Enrolled patients were outpatients under asthma treatment by Maebashi North Hospital and Gunma University Hospital, or visited Maebashi North Hospital and Gunma University Hospital for the reason of difficult to control asthma from another hospital. Thirty asthma patients agreed to participate in the two-group, randomized prospective study of the effects of acid suppression on asthma symptoms using an H2 blocker and a PPI. Six patients were enrolled in Maebashi North Hospital, and twenty-four patients were enrolled in Gunma University Hospital. Patients were randomly and blindly assigned to oral treatment with either the H2 blocker roxatidine (150 mg/day) or the PPI lansoprazole (30 mg/day) for 2 months. The dose of 30 mg lansoprazole was the same dose as recommend for GERD control dose by previous report (Kiljander 2003). They underwent endoscopic examination, and the QUEST score was determined. Patients enrolled in the randomized study had GERD symptoms (QUEST ≥ 4) and/or an endoscopic examination showing Grade ≥ M. The changes in the QUEST score, the asthma symptom score, PEF, FEV1.0, and non-specific IgE assayed by radio immunosorbent test (RIST) (normal upper limit, 250 IU/ml) were evaluated before and after two months of therapy. Patients recorded PEF for two weeks prior to starting the medication, and then recorded PEF every day after starting. The asthma treatment regimen was not changed during the first two months of the study period. To check for any adverse effects of acid suppressive treatment, the white blood count (WBC), the red blood cell count (RBC), aspartate
aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase isozyme (LDH), blood urea nitrogen (BUN), Cr, Na, K and Cl, were measured before and after the study. The study was conducted according to the guidelines of the Declaration of Helsinki, and all patients gave written informed consent before enrollment in the study. Approval for this study was given by the Human Research Committee of Maebashi North Hospital and Gunma University Institution. This study was started from June 1, 1998 in Maebashi North Hospital, and started from August 1, 2000 in Gunma University Hospital.

Statistical analysis

All values are shown as means ± S.D. The difference between two groups were tested using $2 \times 2$ Chi-square test with Yates’s test applied to adjust data where the sample number was < 10. Changes in the PEF and asthma symptom score before and after drug administration were tested using the Wilcoxon t-test. Statistical significance was set at $p < 0.05$.

RESULTS

The patient characteristics for each group are shown in Table 2; no differences in age, gender, LA grades and asthma grades were observed between the two groups. Enrolled asthma patients with grade N had GERD symptoms evaluated by QUEST score $\geq 4$. The randomized study of roxatidine and lansoprazole showed that before treatment, a QUEST score $\geq 4$ was obtained in 10/15 (66.7%) roxatidine-treated patients and in 11/15 (73.3%) lansoprazole-treated patients ($p = ns$, Table 1). The pre-treatment QUEST score was 8.1 ± 4.9 (mean ± S.D.) in the roxatidine-treated group and 8.3 ± 4.9 (mean ± S.D.) in the lansoprazole-treated group (Fig. 1). After treatment, the QUEST score was 4 ± 3.6 (mean ± S.D.) in the roxatidine-treated group and 2.4 ± 2.8 (mean ± S.D.) in the lansoprazole-treated group. In both groups, the QUEST scores showed significant improvement with treatment ($p < 0.05$). Before treatment, PEF was 321.5 ± 161.3 (mean ± S.D.) in the roxatidine-treated group and 323.1 ± 119.3 (mean ± S.D.) in the lansoprazole-treated group (Fig. 2). After treatment, the PEF was 334.9 ± 141.2 (mean ± S.D.) in the roxatidine-treated group and 353.3 ± 119.4 (mean ± S.D.) in the lansoprazole-treated group. Two months of lansoprazole therapy significantly improved PEF ($p < 0.05$), but roxatidine therapy did not significantly improve PEF. Before the treatment, the PEF was not significantly different between the roxatidine-
Table 2. Patients characters. Patients characters between groups in age, gender (M/F), LA grades and asthma grades were not significantly different. The difference between two groups were tested using $2 \times 2$ Chi-square test with Yates’s test applied to adjust data where the sample number was $< 10$.

<table>
<thead>
<tr>
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<th>Roxatidine (H₂ blocker) group</th>
<th>Lansoprazole (PPI) group</th>
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<tbody>
<tr>
<td>Age (mean ± s.d.)</td>
<td>59 ± 15</td>
<td>56 ± 11</td>
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<tr>
<td>M/F (pt number)</td>
<td>7/8</td>
<td>6/9</td>
</tr>
<tr>
<td>LA Grade (number of patients)</td>
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</tr>
<tr>
<td>N</td>
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<td>M</td>
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<td>D</td>
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<td>Asthma grades (number of patients)</td>
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<td>Step 1</td>
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Fig. 1. QUEST score changes before and after roxatidine and lansoprazole treatment in asthmatic patients. Statistically significant differences before and after treatment are expressed by $^*p < 0.05$. 
treated and lansoprazole-treated groups. ACQ scores were improved in lansoprazole group, and FEV$_{1.0}$ and IgE were not affected by roxatidine or lansoprazole treatment (Table 3). The asthma treatment score was decreased in the lansoprazole-treated group ($p < 0.05$), but the score was not decreased in the roxatidine-treated group. Blood test results, including WBC, RBC, AST, ALT, LDH, BUN, Cr, Na, K and Cl were not affected by either treatment, and no adverse effects were noted with either treatment.

**DISCUSSION**

We tested whether acid suppressive medication contributed to an improvement of asthma. GERD symptoms, evaluated by the QUEST score, were ameliorated in both the roxatidine-treated and lansoprazole-treated patients (Fig. 1), but PEF

![Fig. 2. PEF changes before and after roxatidine and lansoprazole treatment in asthmatic patients. Statistically significant differences before and after treatment are expressed by $^* p < 0.05$.](image)

**Table 3.** Changes of FEV$_{1.0}$, IgE levels, asthma symptoms evaluated by ACQ. Changes in the PEF and asthma symptom score before and after drug administration were tested using the Wilcoxon $t$-test. Statistical significance was set at $p < 0.05$.

<table>
<thead>
<tr>
<th></th>
<th>Roxatidine (H$_2$ blocker) group</th>
<th>Lansoprazole (PPI) group</th>
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</thead>
<tbody>
<tr>
<td>FEV$_{1.0}$ before (ml)</td>
<td>1,839.7 ± 880.7</td>
<td>1,993.3 ± 850.1</td>
</tr>
<tr>
<td>FEV$_{1.0}$ after (ml)</td>
<td>2,003.3 ± 883.4</td>
<td>2,057.4 ± 927.8</td>
</tr>
<tr>
<td>IgE before (IU/ml)</td>
<td>239.0 ± 251.2</td>
<td>281.6 ± 289.3</td>
</tr>
<tr>
<td>IgE after (IU/ml)</td>
<td>240.9 ± 248.1</td>
<td>286.0 ± 302.7</td>
</tr>
<tr>
<td>ACQ before (mean ± S.D.)</td>
<td>12.3 ± 2.1</td>
<td>14.4 ± 4.2</td>
</tr>
<tr>
<td>ACQ after (mean ± S.D.)</td>
<td>9.0 ± 3.1</td>
<td>9.4 ± 4.2</td>
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![Image](image)
Proton Pump Inhibitor, Lansoprazole, in Asthma Symptoms with GERD

and asthma symptoms were improved only in the lansoprazole-treated group (Fig. 2, Table 3). Both roxatidine and lansoprazole have been shown to improve reflux symptoms in patients with GERD by more than 90% (Friedrich et al. 1996; Malagelada et al. 2004). However, endoscopic healing rates do not necessarily correspond with symptom improvement rates (Friedrich et al. 1996). PPIs have a greater effect on acid suppression than H$_2$ blockers and are highly effective for acute healing of erosive esophagitis; in fact, they are the only class of drug that minimizes relapse of esophagitis (Chiba 1997). These differences may be responsible for the different results obtained in the roxatidine-treated and lansoprazole-treated groups with respect to PEF improvement, asthma symptom improvement, although both drugs improved GERD symptoms evaluated by QUEST. Changing from an H$_2$ blocker to a PPI has been shown to increase PEF (Tsugeno et al. 2003), which is in agreement with our results. These indicate that the PPI is superior to the H$_2$ blocker for treating asthmatic patients with GERD. The present study showed lansoprazole increased PEF and improved asthma symptoms, but the degree was slightly increasing about 20 L/min. This implies clinical relevance of PPI in increase of PEF is not so much in dilatation of bronchus, and PPI treatment contributes to asthma symptoms improvement on asthma patients with GERD. Consistent with a previous report (Field and Sutherland 1998), the present study has shown that FEV$_{1.0}$ was not improved in asthmatic patients treated with a H$_2$ blocker or a PPI. Kiljander et al. (2003) suggested that FEV$_{1.0}$ was not improved in asthmatic patients because they had good asthma control before PPI treatment, and relatively severe GERD was due to insufficient PPI treatment. However, in the present study, the severity of asthma was variable, and GERD severity was also variable (Table 2). As in previous reports, we found that PPI treatment did not affect FEV$_{1.0}$ (Kiljander 2003).

Recently, large multi-center trial evaluating the effects of esomeprazole (40 mg b.i.d) on asthma had been completed, showing significant improvement in asthma symptom scores and PEF only in patients with GERD and nocturnal respiratory symptoms (Kiljander et al. 2006). Legget et al. (2005) have reported that in patients with difficult-to-control asthma, GERD was common, but the identification and treatment of GERD did not appear to improve asthma control. Boeree et al. (1998) have reported that high-dose PPI treatment had no effect in patients with severe airway hyper-responsiveness and symptomatic GERD. The severity of GERD and the severity of asthma seem to be two important factors when evaluating the effects of acid suppressive medication on asthma in asthmatic patients with GERD.

Elevation of IgE indicates presence of atopy or allergy to drugs (Gina 2003). IgE levels in present study were unchanged in both groups of patients treated with roxatidine or lansoprazole, suggesting that acid suppressive drugs did not cause IgE-mediated drug allergy in asthma patients in present study. In the enrolled asthma patients, IgE levels were not elevated, unlike atopic asthma with IgE elevation.

A recent report has shown that gastric acid-suppressive therapy was associated with an increased risk of community-acquired pneumonia (Laheij et al. 2004). However, the treatment duration and the dosage of PPI therapy in asthmatic patients with GERD still need to be addressed. Previous studies have recommended the high-dose therapy for 2 to 3 months (Harding and Sontag 2000; Harmanci et al. 2001). Exogenous airway acidification by GERD or acid fogs were important factors in the deterioration of asthma, contributed to a decrease in pH with airway inflammation, and altered immune cell function. Taken together, the airway pH homeostasis could be a new target for therapy (Ricciardolo et al. 2004). Thus, PPI therapy is needed to avoid airway acidification in patients with asthma, but the duration and dosage of PPI treatment remains to be determined keeping an airway homeostasis without increase in the risk of pneumonia in asthmatic patients with GERD.

In conclusion, to effectively treat asthmatic patients with GERD, we need to elucidate the pathogenesis of asthma with GERD, the rates of the various asthma outcomes with PPI therapy,
and how to use intermittent PPI therapy. Further research will be needed to determine the place of PPI in asthma treatment guideline.

Acknowledgments

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References


