Original Article

Effects of omeprazole and cisapride treatment in Japanese asthmatics with reflux esophagitis

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ABSTRACT

In the United States and Europe, gastroesophageal reflux (GER) is receiving attention as a potential cause of bronchial asthma. Few Japanese case reports have described this relationship. Therefore, we investigated the effect of omeprazole and cisapride on pulmonary function tests, blood gases and home peak expiratory flow rates (PEFR) in six Japanese outpatients with asthma and proven GER. After 8 weeks of treatment, reflux esophagitis had improved in all patients. However, the parameters of pulmonary function showed no change other than a significant post-treatment increase in home PEFR (4.4–27.7%) in three patients. These results suggest that anti-reflux (omeprazole and cisapride) treatment will produce small improvements in the PEFR in some Japanese asthmatics with GER.

Key words: bronchial asthma, cisapride, gastroesophageal reflux, Japanese, omeprazole, reflux esophagitis.

INTRODUCTION

In the United States and Europe, gastroesophageal reflux (GER) has been demonstrated in approximately 40% of asthma patients.1,2 However, in Japan, few case reports have provided details regarding the relationship between these two factors.3 We have diagnosed GER in six of 21 perennial asthma patients (29%) via fiberoptic esophagoscopy.4 We have also reported that many patients with asthma and concurrent GER have not been diagnosed. The body mass index (BMI) and gastric acid pH, which are closely related to the risk of GER,5 differ among races.6,7 We therefore considered that investigation of the relationship between bronchoconstriction and GER in Japanese asthma patients was justified.

There have been some reports of pulmonary function data and peak expiratory flow rates (PEFR) obtained during histamine H2 receptor antagonist treatment in asthma patients with GER, but these results have been controversial.8,9 Histamine H2 receptor antagonists, particularly cimetidine, alter the clearance of theophylline,10–13 which may have been responsible for the differences in these results.

Omeprazole and cisapride have been used in the treatment of reflux esophagitis. Omeprazole has been shown to give reliable and effective 24 h control of acid secretion. This gives rapid symptom relief and healing in patients with reflux esophagitis.14 Cisapride enhances gastrointestinal motility by increasing the release of acetylcholine via the 5-hydroxytryptamine receptor in humans.15 These drugs have not been known to influence the serum theophylline concentration. The present paper reports the effects of reflux esophagitis therapy, consisting of omeprazole and cisapride (not histamine H2 receptor antagonists), on pulmonary function tests, blood gases and home PEFR in Japanese asthma patients treated as outpatients.

METHODS

Subjects

Potential subjects included patients referred to the Department of Internal Medicine at Niigata Prefectural
Kakizaki Hospital and diagnosed with bronchial asthma and reflux esophagitis between January and December 1993. Of these patients, those who periodically recorded their PEFR in the early morning and evening were selected for this study. All patients were non-smokers with symptoms of reflux. Bronchial asthma was diagnosed by a history of episodic dyspnea with wheezing and reversible increases in the forced expiratory volume in 1 s (FEV₁) of more than 20%, either spontaneously or after medication.¹⁶ No subject with bronchial asthma had had any attacks during the 6 week period prior to the study. In addition, no subject had a history of respiratory tract infection for 6 weeks prior to the study. Asthma severity was classified according to the Global Strategy for Asthma Management and Prevention.¹⁷ Informed consent was obtained from each subject prior to the start of the study, which was approved by the Institute’s Committee on Clinical Research.

**Diagnostic methods**

Each diagnosis of esophagitis, confirmed by esophagoscopy and histopathologic examination of esophagoscopic biopsy findings, was evaluated by two or more gastroenterologists. Reflux esophagitis was classified according to the criteria of Savary and Miller.¹⁸

The forced vital capacity (FVC), FEV₁, V₂₅/body height (V₂₅/Ht) and arterial blood gas values (oxygen tension (PₐO₂), carbon dioxide tension (PₐCO₂), alveolar–arterial oxygen tension gradient (A-aDO₂)) were also measured in asthma patients with evidence of reflux esophagitis.

Pulmonary function was determined using a hot-wire flow meter (Autospiro AS-7; Minato Corp., Tokyo, Japan). Blood gas analysis was performed as follows: after patients had rested in a supine position for longer than 15 min, blood samples were obtained from the brachial artery and were heparinized prior to injection into an automatic pH blood gas analyzer (Ciba Corning 278; Ciba-Corning Diagnostic Corp., Tokyo, Japan). The PₐO₂ and PₐCO₂ were measured in each sample. According to the method of Comroe,¹⁹ the ideal alveolar oxygen tension was calculated from the PₐCO₂. The A-aDO₂ was calculated by subtracting PₐO₂ from the ideal alveolar oxygen tension.

Peak expiratory flow rates from the early morning and evening, which had been periodically recorded in asthma patients’ diaries for 2 weeks prior to the study, were obtained. The patients were provided with a Wright mini-peak flow meter (Clement Clark International Ltd, Harlow, UK). Three peak flow readings were taken at three time points and the highest value was entered on a diary card. Patients recorded their PEFR twice a day during omeprazole and cisapride treatment.

Patients were also given an 8 week supply of omeprazole (20 mg/day) and cisapride (7.5 mg/day) tablets. Patients continued their conventional asthma therapy. After 8 weeks of treatment, the FVC, FEV₁, V₂₅/Ht, PₐO₂, and A-aDO₂ were reassessed and repeat esophagoscopy was performed.

**Statistical analysis**

Pre- and post-treatment FVC, FEV₁, V₂₅/Ht, PₐO₂, and A-aDO₂ values were compared along with weekly summed PEFR. Results are expressed as the mean±SD. Statistical analysis was performed using the Wilcoxon rank sum test. A P value of <0.05 was considered statistically significant.

**RESULTS**

All six patients who entered the study, completed the trial period. The subjects included four men and two women with a mean age of 53 years (range 33–61 years). All suffered perennial asthma attacks. Four patients had atopic disease and two had non-atopic disease. All patients were classified with moderate asthma (Table 1). They were managed with oral theophylline (500–700 mg/day), an inhaled steroid (beclomethasone dipropionate, 400–800 μg/day) and a short-acting inhaled β₂-adrenoceptor agonist (procaterol hydrochloride; 10–60 μg/day). Three patients took an oral β₂-adrenergic drug (procaterol hydrochloride; 50–100 μg/day; Table 2).

There was no difference in the frequency of the use of inhaled bronchodilators or other asthmatic therapy between pre- and post-treatment periods. Asthma symptoms in all six patients, such as cough, chest tightness, wheezing and dyspnea, did not worsen.

Pre- and post-treatment FVC, FEV₁, V₂₅/Ht and blood gas values did not differ significantly (Table 3). Classification of reflux esophagitis according to the criteria of Savary and Miller¹⁸ showed that four patients had stage I disease and two had stage II disease. All cases of reflux esophagitis improved after treatment. Figure 1 shows the early morning and evening PEFR values obtained during the 8 weeks of omeprazole and cisapride treatment and during the preceding 2 week interval. Peak expiratory flow rates performed at similar
Table 1. Subject characteristics

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Sex</th>
<th>Body height (m)</th>
<th>Bodyweight (kg)</th>
<th>BMI (kg/m²)</th>
<th>Asthma type</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>SS</td>
<td>M</td>
<td>1.65</td>
<td>63</td>
<td>23</td>
<td>Perennial atopic</td>
<td>Moderate</td>
</tr>
<tr>
<td>YK</td>
<td>M</td>
<td>1.70</td>
<td>74</td>
<td>26</td>
<td>Perennial atopic</td>
<td>Moderate</td>
</tr>
<tr>
<td>OH</td>
<td>M</td>
<td>1.65</td>
<td>70</td>
<td>26</td>
<td>Perennial atopic</td>
<td>Moderate</td>
</tr>
<tr>
<td>AY</td>
<td>F</td>
<td>1.40</td>
<td>42</td>
<td>21</td>
<td>Perennial non-atopic</td>
<td>Moderate</td>
</tr>
<tr>
<td>MM</td>
<td>F</td>
<td>1.43</td>
<td>46</td>
<td>22</td>
<td>Perennial non-atopic</td>
<td>Moderate</td>
</tr>
<tr>
<td>MK</td>
<td>M</td>
<td>1.60</td>
<td>57</td>
<td>22</td>
<td>Perennial atopic</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

BMI, body mass index; M, male; F, female.

Table 2. Subject characteristics

<table>
<thead>
<tr>
<th>Asthma duration (years)</th>
<th>Serum IgE (IU/L)</th>
<th>Blood eosinophil counts (cells/mm³)</th>
<th>Theophylline</th>
<th>Inhaled steroids</th>
<th>Oral β₂ adrenergic drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>SS</td>
<td>5</td>
<td>258</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>YK</td>
<td>45</td>
<td>293</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>OH</td>
<td>20</td>
<td>246</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>AY</td>
<td>7</td>
<td>114</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>MM</td>
<td>6</td>
<td>64</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>MK</td>
<td>15</td>
<td>436</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Table 3. Pulmonary function parameters before and after omeprazole and cisapride treatment in six asthma patients with reflux esophagitis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before treatment</th>
<th>After treatment</th>
<th>Statistical analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (L)</td>
<td>3.40±0.87</td>
<td>3.50±0.87</td>
<td>NS</td>
</tr>
<tr>
<td>FEV₁₀ (L)</td>
<td>2.33±0.71</td>
<td>2.32±0.63</td>
<td>NS</td>
</tr>
<tr>
<td>V₅₅/body height (L/s per m)</td>
<td>0.37±0.18</td>
<td>0.37±0.16</td>
<td>NS</td>
</tr>
<tr>
<td>PₐO₂ (Torr)</td>
<td>83.5±8.8</td>
<td>86.4±6.4</td>
<td>NS</td>
</tr>
<tr>
<td>A-aDO₂ (Torr)</td>
<td>13.2±6.0</td>
<td>9.8±7.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

FVC, forced vital capacity; FEV₁₀; forced expiratory volume in 1 s; PₐO₂, arterial oxygen tension; A-aDO₂, alveolar–arterial oxygen tension gradient; NS, not significant.

Fig. 1 Peak expiratory flow rates (PEFR) in the early morning (●) and evening (○) before and after treatment with omeprazole and cisapride. Pre- and post-treatment PEFR did not differ significantly. Values are presented as the mean±SD.

DISCUSSION

Suffering from reflux symptoms is an essential feature of GER. Jenkinson et al. have reported that both reflux symptoms and associated endoscopic findings could be
Fig. 2 (a) Three representative patients showed improved morning (●) and evening (○) peak expiratory flow rates (PEFR) after treatment with omeprazole and cisapride. (b) Two patients revealed decreased PEFR and one patient showed unchanged PEFR at both times of the day after anti-reflux treatment. *P<0.05, **P<0.01, ***P<0.005.

detected in their patients with GER. In the present study of Japanese asthmatics with reflux esophagitis indicative of GER, there were no significant changes in FVC, FEV\textsubscript{1.0}, V\textsubscript{50}/Ht, PEFR, PaO\textsubscript{2} or A-aDO\textsubscript{2} during pre- and post-omeprazole and -cisapride treatment followed by the usual asthma therapy. However, reflux esophagitis improved in all patients. Three of six patients showed a significant increase in home PEFR.

Goodall et al.\textsuperscript{8} have performed a double-blind crossover study comparing asthma symptoms, pulmonary function test data and home PEFR values in 20 patients with asthma and GER receiving cimetidine therapy or a placebo. Asthma symptoms and PEFR in patients treated with cimetidine for 6 weeks improved significantly in comparison with placebo. However, other pulmonary function data between cimetidine and placebo treatment groups did not differ significantly. Ekström et al.\textsuperscript{9} also compared 4 weeks of ranitidine therapy with 4 weeks of placebo in 48 asthma patients. Respiratory and reflux symptoms decreased significantly with ranitidine therapy, but pulmonary function data, home PEFR values and bronchial sensitivity did not change significantly.
According to these two reports, the effects of histamine H₂ receptor antagonists on asthma symptoms and pulmonary function data are similar, but improvement in home PEFR is controversial. Histamine H₂ receptor antagonists, particularly cimetidine, alter theophylline clearance, causing an increase in the serum theophylline concentration.10-13 Goodall et al.8 did not mention whether their subjects were taking theophylline. If their subjects had been taking theophylline during cimetidine treatment, the serum theophylline concentration may have increased, influencing the PEFR. In addition, Ekström et al.9 have reported that 26 of their 48 subjects were taking theophylline. In the present study, omeprazole and cisapride treatment were used instead of a histamine H₂ receptor antagonist, thus avoiding the influence of potential changes in the serum theophylline concentration induced by cimetidine.

There has been no report of omeprazole or cisapride influencing the serum theophylline concentration, directly affecting the bronchomotor tone or inducing bronchodilation. In four of six patients in the present study, the serum theophylline concentration was measured before and after omeprazole and cisapride treatment and was not different before and after treatment (10.9±4.7 vs 9.2±5.6 µg/mL, respectively). Therefore, we conclude that omeprazole and cisapride treatment effectively increases gastric acid pH and decreases GER without influencing theophylline concentration. The result of no significant difference between pre- and post-treatment PEFR was consistent with the results of the study of Ekström et al.9 Our study subjects were stable asthmatics without symptoms during the preceding 6 weeks. The mean age of the patients in the study of Ekström et al.9 was 59 years and their mean FEV₁, was 2.26 L. Thus, the degree of bronchoconstriction in the patients in the study of Ekström may have been similar to that in our subjects at the onset of the study. In contrast, different degrees of bronchoconstriction at the onset of the study (an FEV₁, of 62% recorded by Goodall et al.8 compared with an FEV₁,<FVC (2.33/3.40) of 69% in the present study) may have accounted for the different results between our study and that of Goodall et al.

In addition, gastric acid pH and degrees of obesity, which are both related to GER, differ among races.4,5 Therefore, we believe that differences among the subjects studied and the therapeutic agents used (H₂ receptor antagonists vs omeprazole and cisapride) between these three studies may be related to the different results observed.

With regard to the etiology of GER-induced asthma attacks, two hypotheses have been proposed. One involves the microaspiration of hydrochloric acid into the lungs due to GER.21-23 The other involves bronchoconstriction caused by vagal reflexes from the esophagus, trachea and bronchi, enhanced by stimulation of the esophageal mucosa due to hydrochloric acid.24,25 It is difficult to draw definitive conclusions regarding the mechanisms underlying GER-induced asthma attacks. Previously, we have reported three patients with a GER-induced cough diagnosed by bronchial biopsy as having chronic airway inflammation accompanied by a lymphocytic infiltration.26,27 Therefore, we speculate that repeat tracheobronchial microaspiration of reflux gastric acid or vagally mediated reflux may cause chronic inflammatory damage to the bronchial mucosa and resultant asthmatic attacks.

In the present study the peak flow improvements were minor and probably of little clinical significance in our Japanese asthma patients with reflux esophagitis. Our study sample size was small, therefore, no definite conclusions can be drawn. In Japan, further study is needed to investigate the mechanism of GER-induced asthma.

REFERENCES
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