

Original article

Observational study of omeprazole for gastroesophageal reflux on pulmonary function in adult asthmatics

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Background: Asthma is a chronic inflammatory disease of airways. Gastroesophageal reflux disease (GERD) is known to be associated with worsening asthma. We hypothesized that treatment of GERD in asthmatics will improve asthma control and quality of life. We reviewed our experience of treatment of GERD in asthmatics in Thailand.

Objectives: To study the effects of omeprazole for treatment of GERD in patients with poorly controlled asthma on pulmonary function tests and asthma control test (ACT) scores.

Methods: This study was conducted at King Chulalongkorn Memorial Hospital between August 2009 and December 2010. Patients with partly controlled and uncontrolled asthma who were found to have GERD by 24 hour esophageal pH monitoring were administered omeprazole 40 mg per day for 8 weeks. Pulmonary function tests and ACT scores before and after treatment were compared at 4-weeks and 8-weeks follow up.

Results: Twenty four patients were included in this study. None of them had asthmatic attacks during the study. After 4 and 8 weeks of omeprazole treatment, the mean FEV₁ (2.20 ± 0.64 L, 2.36 ± 0.58 L, respectively) and the mean ACT score (20.82 ± 3.30 , 23.00 ± 1.69 , respectively) were significantly higher than the pretreatment values (mean FEV₁ 1.99 ± 0.56 L and ACT score 16.36 ± 3.97) ($P < 0.05$).

Conclusion: High-dose omeprazole may improve pulmonary function and the level of asthma control in Thai patients with partly controlled or uncontrolled asthma and coexisting GERD.

Keywords: Asthma, GERD, pulmonary function test, omeprazole, symptom assessment

Asthma is a chronic inflammatory disease of the airways that causes airway hyperresponsiveness, cough, dyspnea and wheezing [1]. Asthma prevalence has increased worldwide [2]. The reported prevalence of asthma in Thai population is 10%–12% in children and 6.9% in adults [3-5]. More than half of the patients were unable to maintain their normal routine activities, 21.7% required medical emergency room visits and 14.8% required hospital admission [6]. Previous studies have found that acid reflux was an important factor associated with poorly controlled asthma [7]. Prevalence of GERD in patients with asthma was found to be as high as 34%–80% [8, 9]. Furthermore,

the symptoms of asthma were found to correlate with gastroesophageal acid refluxes as measured by 24-hr pH monitoring [10]. Studies of the relationship between GERD treatment and proton-pump inhibitors (PPIs) and asthma control have been produced inconsistent results [11-14]. We could not find data from Thailand of the effect of GERD treatment with high doses omeprazole on lung function in Thai asthmatics.

Methods

We conducted this pre- and post-treatment study in Thai patients with high-dose oral omeprazole (20 mg twice a day) whose asthma was partly controlled or uncontrolled. Inclusion criterion were (1) age of 18–70 years; (2) were diagnosed as having asthma, which was supported by either documentation of a 12% and 200 mL increase in FEV₁ after use of a bronchodilator or a positive methacholine challenge

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test; (3) at least 4 weeks of stable use of an inhaled corticosteroid at a dose equivalent to 400 µg or more; (4) partly controlled and uncontrolled asthma as defined by GINA guideline 2008 [15]. Participants were excluded if they had any of the followings: (1) smoked cigarettes within the previous 6 months; (2) denied 24 h esophageal pH monitoring; (3) other lung diseases; (4) use of antireflux medication within the previous 7 days; or (5) use of drugs that could interact with PPIs. Participants were also excluded if they were pregnant, unable to tolerate PPIs, or had any serious illness that would interfere with participation in the study. All participants provided written informed consent. The study was approved by the Institutional Review Board (IRB) of the Faculty of Medicine, Chulalongkorn University (IRB approval No. 111/52).

Study design

This study was conducted from August 2009 through December 2010. It was designed as a pre- and post-comparison observational study to test the hypothesis that omeprazole could improve pulmonary function and ACT scores in partly controlled or uncontrolled asthmatics. Participants who met the eligibility criteria were enrolled in a 4 study period during which time they completed baseline daily asthma diaries and underwent esophageal pH testing. All participants underwent chest radiography, pulmonary function tests, and ACT scoring at baseline. They received 20 mg of omeprazole orally twice a day for 8 weeks. The reassessments of pulmonary

function and ACT score were performed at 4th and 8th weeks of treatment. All patients gave their documented informed consent to participate and understood that results of this observational study would be published without identifying any of the participants.

Data analysis

We calculated that with a sample size of 27 participants, the study would have 80% power, with a two-sided type I error rate of 5%, in order to show a difference of 20% in the mean of FEV₁. The primary outcome was a mean difference of FEV₁ before and after treatment of GERD. The secondary outcome was a mean difference of ACT score before and after treatment of GERD. We analyzed data by using a paired *t* test and considered *P* < 0.05 as significant.

Results

Sixty-five qualified participants were enrolled from the outpatient clinic at King Chulalongkorn Memorial Hospital between August 2009 and December 2010. All underwent 24 hr pH monitoring. Twenty-four participants (37%) were found to have GERD and were consecutively enrolled in the study (**Figure 1**). Twelve (50%) were male. Mean age was 51.92 ± 10.71 years (mean \pm SD). None had asthma exacerbation as defined as a progressive increase in shortness of breath, cough, wheezing or chest tightness, or a combination of these symptoms during the study period (**Table 1**).

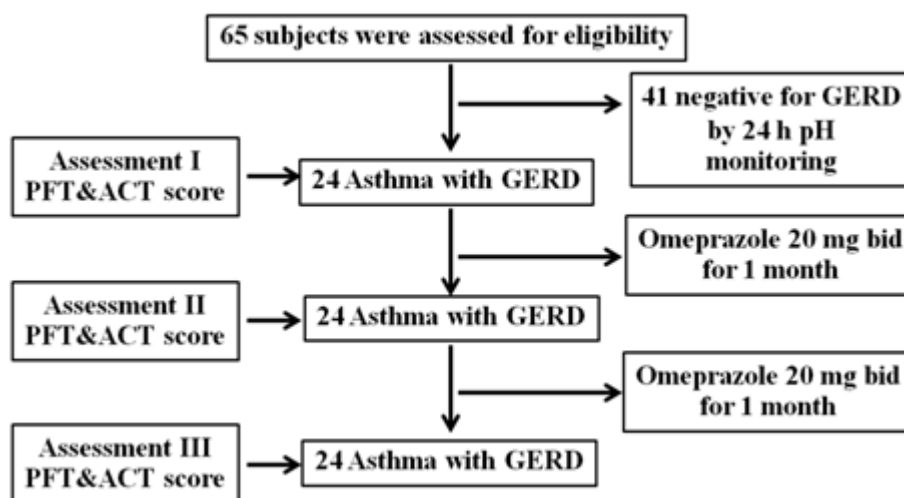


Figure 1. Flow of the patients through the study

Table 1. Baseline characteristics

Characteristic	Value (%)
Number of patients	24
Male sex, no (%)	12 (50)
Age, years	
mean \pm SD	51.92 \pm 10.71
range	31–70
Male age, year	53.17 \pm 10.95
Female age, year	50.67 \pm 10.78
Body mass index, kg/m ²	22.07 \pm 4.79
Symptomatic GERD, no (%)	18 (75)
regurgitation	18 (100)
heartburn	15 (83)
chest pain	13 (72)
chronic cough	10 (55)
hoarseness	8 (44)
Asthma control status, no (%)	
partly controlled	18 (75)
uncontrolled	6 (25)
Medication, no (%)	
SABA+ICS	7 (29)
SABA+LABA/ICS	12 (50)
SABA+LABA/ICS+theophylline	4 (17)
SABA+LABA/ICS+theophylline+antileukotriene	1 (4)
Coexisting conditions, no (%)	
allergic rhinitis	8 (33)
hypertension	6 (25)
avascular necrosis	1 (4)
diabetes mellitus	3 (12)
benign prostate hypertrophy	1 (4)
dyslipidemia	3 (13)
ACT score, no (%)	
20–24	8 (33)
<20	16 (67)
Smoking status	0 (0)

GERD = gastroesophageal reflux disease, SABA = short-acting β 2 agonist, ICS = inhaled corticosteroid, LABA = long-acting β 2 agonist, ACT = asthma control test

Among 24 asthmatics who were found to have GERD, 18 had GERD symptoms. Of these patients, 18 had regurgitation, 15 heartburn, 13 chest pain, 10 chronic cough, and 8 hoarseness of voice, respectively. Eighteen patients were partly controlled asthmatics.

Regarding asthma medications, short-acting β 2-agonist and long-acting β 2-agonist plus inhaled corticosteroid (SABA + LABA/ICS) was the mostly commonly used regimen (12 patients) while SABA + LABA/ICS + theophylline + antileukotriene was the least used regimen (1 patient). Allergic rhinitis was found in 8 patients.

Baseline ACT score was lower than 20 in 16 patients (66%).

There were no patients with exacerbation of asthma throughout the study period. The FEV₁, FVC, PEF, and ACT scores were significantly improved with omeprazole administration as shown in **Table 2**. Likewise, there was no sex difference in terms of the improvements of FEV₁, FVC, PEF and ACT score after omeprazole treatment (**Table 3**).

At the end of the study, most participants (71%) had improvement of asthma and none had worsening of their asthma (**Figure 2**). GERD symptoms had resolved in most case (89%) and the rest of the

participants had some improvement. All patients with improved asthma control had improvement of their GERD symptoms. The patients with improvement of asthma status tended to be less obese, compared with

patients whose asthma status remained unchanged (BMI of 20.04 ± 2.55 vs. 22.94 ± 3.32 kg/m², respectively; $P = 0.06$).

Table 2. Pulmonary function and ACT score after treatment 1 and 2 months

Variables	Baseline	4 th week	8 th week
FEV ₁	1.99 ± 0.56	$2.20 \pm 0.64^*$	$2.36 \pm 0.58^*$
FVC	2.84 ± 0.74	$3.05 \pm 0.81^{**}$	$3.13 \pm 0.82^*$
PEF	338.64 ± 109.60	$365.0 \pm 103.0^{**}$	$399.47 \pm 101.79^*$
ACT	16.36 ± 3.97	$20.82 \pm 3.30^*$	$23.00 \pm 1.69^*$

Data expressed as mean \pm SD, * $P < 0.001$ vs. baseline, ** $P < 0.05$ vs. baseline

FEV₁ = forced expiratory volume in one second, FVC = forced vital capacity, PEF = peak expiratory flow, ACT = asthma control test

Table 3. Gender differences and the improvement of pulmonary function and ACT score after treatment

Variables	Baseline	4 th week	8 th week
FEV ₁ (L)			
Male	2.20 ± 0.48	$2.46 \pm 0.50^*$	$2.55 \pm 0.49^*$
Female	1.74 ± 0.52	$1.91 \pm 0.61^{**}$	$2.05 \pm 0.51^{**}$
FVC (L)			
Male	3.21 ± 0.63	3.41 ± 0.68	$3.46 \pm 0.71^{**}$
Female	2.43 ± 0.56	$2.68 \pm 0.70^{**}$	$2.75 \pm 0.60^*$
PEF (L/min)			
Male	378.33 ± 79.07	$403.33 \pm 78.89^{**}$	$430.83 \pm 68.02^*$
Female	295.83 ± 114.85	$322.50 \pm 103.14^{**}$	$341.67 \pm 104.26^*$
ACT score			
Male	17.08 ± 3.29	$21.67 \pm 1.92^*$	$23.42 \pm 1.31^*$
Female	15.50 ± 4.66	$20.08 \pm 4.03^*$	$22.83 \pm 1.85^*$

Data expressed as mean \pm SD, * $P < 0.001$ vs. baseline, ** $P < 0.05$ vs. baseline

FEV₁ = forced expiratory volume in one second, FVC = forced vital capacity, PEF = peak expiratory flow, ACT = asthma control test

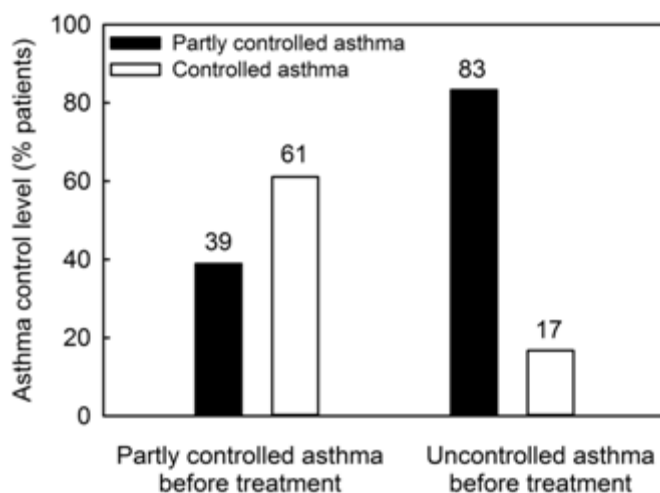


Figure 2. Change in asthma control level after omeprazole treatment. Solid bars indicate partly controlled asthma after treatment, and open bars indicate controlled asthma after treatment.

Discussion

Achieving a good control of asthma is difficult in some GERD patients. Avoidance of stimuli, using the asthma drug correctly and treatment of comorbid diseases can improve control of asthma. GERD is a condition that is known to be associated with asthma and the two may coexist. Prevalence of GERD in asthmatics was documented to be as high as 34%–80% [8, 9] compared with subjects without GERD where it is 5%–10% [16]. Previous studies have shown that GERD is a factor that can worsen asthma control [16–21]. This can be explained by 3 processes, including increased vagal tone, heightened bronchial reactivity, and microaspiration of gastric content.

Our findings are similar to those reported by Kiljander et al. [22] that showed significant prevalence of GERD in asthmatic patients (36%). There have been inconsistent findings with regard to the effect of antireflux therapy on pulmonary function and GERD symptoms. Teichtahl et al. [21] studied 20 asthmatic patients with GERD and showed that using omeprazole 40 mg/day for 4 weeks resulted in significant improvement in PEF. However, there were no significant improvements in daytime symptoms or FEV₁. Kiljander et al. [23] studied 52 asthmatic patients with GERD and found that using omeprazole 40 mg/day for 8 weeks resulted in improvement in night-time symptoms. However, there were no significant improvements in daytime symptoms on PEF or FEV₁. Esomeprazole 40 mg twice daily may improve pulmonary function (FEV₁) and asthma-related quality of life [14]. Harding et al. [19] studied 30 asthmatic patients with GERD and showed that using omeprazole 40 mg/day for 12 weeks, did not result in improvement in any of the parameters including daytime symptoms, night-time symptoms, PEF, and FEV₁. Kiljander et al. [24] studied 322 asthmatic patients with GERD and showed that esomeprazole 80 mg/day for 16 weeks resulted in significant improvement in PEF only in patients who had night-time symptoms. The American Lung Association Asthma Clinical Research Center studied 412 partly controlled asthmatics with GERD. Most had no or little symptoms of GERD [25]. The study showed that esomeprazole 80 mg/day for 24 weeks did not result in improvement in lung function, ACT score, nighttime symptoms, or quality of life. Littner et al. [13] studied 207 asthmatics with GERD and showed that lansoprazole 60 mg/day for 24 weeks reduced asthma attack and improved quality of life, but did not improve asthma symptoms or lung function.

These inconsistent findings can be explained by differences in the studied populations and diagnosis of GERD by using symptoms alone—without 24 h pH monitoring. This could result in including patients whose GERD symptoms were not associated with real acid reflux. Thus, the strength of our study is the use of 24 h pH monitoring to diagnose GERD and thus exclude patients without real acid reflux. We also noted that there was no increase in obesity following improvement of asthma control after GERD treatment. The patients remained nonobese at the end of this study (BMI 22.81 ± 5.93 kg/m²), compared with BMI recorded at the beginning of the study (22.08 ± 4.97 kg/m², $P = 0.06$).

We also found some evidence that was concordant with our results, which may be from using the same GERD diagnostic criteria. Sharma et al. [26] studied 99 asthmatics with GERD and showed that omeprazole 40 mg/day with domperidone 10 mg three times before meal for 16 weeks significantly improved daytime symptoms, nighttime symptoms, PEF and FEV₁. Gopal et al. [11] studied 70 asthmatics with GERD and showed that omeprazole 20 mg/day for 4 weeks significantly improved asthma scores and lung function.

One weakness of our study is the small sample size. Although we only included 24 and not the 27 calculated for statistical power, we demonstrated significant improvement in asthma control after GERD treatment. However, the present before and after treatment comparative study may have some inherent bias due to lack of a control group. In addition, the improvement of GERD was solely based on clinical interviews, we did not repeat 24 h pH monitoring after omeprazole treatment.

Conclusion

We have found that there are significant improvements in lung function and quality of life with the use of high dose proton-pump inhibitor (omeprazole) in Thai patients with partly controlled and uncontrolled asthma who were found to have coexisting gastroesophageal reflux.

Acknowledgments

This study was conceived in 2008 and approved by the Institutional Research Committee of Chulalongkorn University. The IRC confirmed that all ethical conditions under the Helsinki declaration had been complied with.

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