RAPID COMMUNICATION

Effect of omeprazole and domperidone on adult asthmatics with gastroesophageal reflux

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ing the mean change from baseline after 16 wk ($P < 0.01$).

CONCLUSION: Combined therapy with Ome and Dom in adult asthmatics with gastroesophageal reflux may be beneficial by reducing asthma symptoms, rescuing medication use, and improving pulmonary function.

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Key words: Asthma; Reflux; Gastroesophageal reflux disease; Antireflux therapy; Prokinetic; Omeprazole

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Abstract

AIM: To study the effect of combined omeprazole (Ome) and domperidone (Dom) therapy on asthma symptoms and pulmonary function in asthmatics with gastroesophageal reflux.

METHODS: We selected 198 asthmatics with gastroesophageal reflux diagnosed by 24-h esophageal pH monitoring to receive Ome 20 mg twice daily and Dom 10 mg three times daily or placebo for 16 wk (1:1 double-blind randomization). Spirometry was done at baseline and after 16 wk of treatment. The primary outcome measures were: mean daily daytime and nighttime asthma symptom scores. Mean daily reflux symptom scores, albuterol use as rescue medication (number of puffs), daytime and nighttime peak expiratory flow rate (PEFR), postbronchodilator forced expiratory volume in 1 second (FEV₁) and postbronchodilator forced vital capacity (FVC) were secondary outcome measures.

RESULTS: Comparison of mean change from baseline between antireflux therapy and placebo groups revealed significant reduction in daytime asthma symptom score (17.4% vs 8.9%), nighttime asthma symptom score (19.6% vs 5.4%), reflux symptom score (8.7% vs 1.6%) and rescue medication use (23.2% vs 3.1%) after antireflux therapy compared to mean change in placebo group ($P < 0.001$). There was significant improvement in morning PEFR (7.9% vs 0.2%), evening PEFR (9.8% vs 0.5%), FEV₁ (11.1% vs 3.78%) and FVC (9.3% vs 1.52%) in the antireflux therapy group compared to placebo on compar-

INTRODUCTION

Gastroesophageal reflux disease (GERD) and asthma are two common diseases that afflict millions of people all over the world. The exact relationship between GERD and asthma has been a source of constant debate. GERD is reportedly the most common trigger in difficult-to-control asthma^[1]. Various mechanisms contributing to GERD exacerbating asthma include a vagus-mediated reflex^[2], a local axonal reflex^[3], heightened bronchial reactivity^[4,5], and microaspiration^[6,7]. GERD is more prevalent in asthmatics compared with control populations and asthmatics frequently associate GERD symptoms with their asthma symptoms. Previous studies have estimated the prevalence of GERD in adult asthmatics at between 34% and 80%^[8-10]. Asthma symptoms also correlated with esophageal pH events on 24-h esophageal pH monitoring^[11].

Previous studies on the effect of antireflux therapy on asthma have shown inconsistent results^[12-24]. Most of these studies have been done in small groups of patients with different proton-pump inhibitors and were done for short durations of anti-reflux therapy. There is limited data on the use of prokinetic agents in asthmatics with GERD^[25] and so far, only one study has explored the effect of a combination of a proton pump inhibitor and a prokinetic agent in asthmatics with GERD^[19]. The present study was done to study the effect of combined therapy with omeprazole, a proton-pump inhibitor and domperidone,

a prokinetic agent on asthma symptoms and pulmonary function in asthmatics with GERD.

MATERIALS AND METHODS

Patients

A total of 410 adult asthma patients attending the outpatient medicine and pulmonary clinics of Lok Nayak Hospital, a tertiary teaching hospital affiliated with Maulana Azad Medical College, University of Delhi, India, were screened after obtaining informed consent. The study was approved by the Institutional Review Board of the hospital. All patients underwent 24-h esophageal pH monitoring to detect GERD. The inclusion criteria of the study at screening included the following: (1) > 18 years of age; (2) > 12% improvement in FEV₁ (in litres) after inhalation of 180 µg of albuterol; (3) mild-to-moderate persistent asthma; (4) no exacerbations or significant change in asthma medications during past weeks of screening; and (5) GERD as diagnosed by 24-hour esophageal pH monitoring. GERD was defined as positive if the total time for which pH was < 4 was > 4.5%^[26]. Exclusion criteria included the following: (1) any unstable chronic medical condition; (2) history of smoking in past or present; (3) history of any other lung disease except asthma; and (4) use of antireflux medications including antacids, histamine-2-receptor antagonists, proton pump inhibitors or prokinetic agents. GERD was diagnosed in 247 asthmatics after 24-h esophageal pH monitoring. Of 247 patients with GERD, 18 patients had history of smoking, 10 patients had history of recent asthma exacerbation, 8 patients were receiving omeprazole therapy, 5 patients were receiving antacids and 2 patients withdrew the consent. After screening, remaining 204 patients for selected for randomization, of which 198 patients completed the study.

Study design

At initial screening (Figure 1), a detailed medical history, physical examination and laboratory tests were done from July 4, 2001 to August 18, 2003 in all asthmatics with GERD who met the inclusion and exclusion criteria. After screening, each patient was given albuterol metered-dose inhaler (Ventolin; Glaxo Smithkline Pharmaceuticals Limited, Mumbai, India) for use as rescue medication, a peak flow meter and a diary. Patients were instructed to record daily daytime and nighttime asthma symptoms, reflux symptoms, morning and evening peak expiratory flow rates more than 3 h after albuterol use and albuterol use as rescue medication. Asthma symptoms included wheezing, chest tightness, dyspnea and cough and were graded on a scale of 0-4 (1-none, 2-mild, 3-moderate, 4-severe). Reflux symptoms included heartburn, regurgitation, dysphagia, belching and hoarseness and were graded similarly. This asthma symptom scale has been used in previous studies^[27-29]. Randomization was done after initial screening and all patients received white capsules containing omeprazole 20 mg (Ome; Dr. Reddy's Laboratories; Hyderabad, India) to be taken orally 1 h before breakfast and 1 h before the evening meal and domperidone (Dom; Dr. Reddy's Laboratories, Hyderabad, India) 10 mg orally 3 times daily (1 h before breakfast, lunch and evening meal) or identical pla-

Figure 1 Study design for GERD therapy.

cebo capsules (1:1 double-blind randomization). We used Ome 20 mg twice daily as this dose has been shown to cause adequate acid suppression in a previous study^[30]. All patients underwent flow-volume spirometry at baseline using standard reference values. Inhaled beta-2 agonists were held for at least 8 h, and oral beta-2 agonists and inhaled anticholinergics were held for at least 12 h before pulmonary function tests. Spirometry was done before and 30 min after inhalation of 180 µg of inhaled albuterol and was repeated after antireflux therapy for 16 wk. The primary outcome measures were: mean daily daytime and nighttime asthma symptom scores. Mean daily reflux symptom scores, albuterol use (number of puffs), daytime and nighttime peak expiratory flow rate (PEFR), postbronchodilator forced expiratory volume in 1 s (FEV₁) and postbronchodilator forced vital capacity (FVC) were secondary outcome measures.

Statistical analysis

Statistical analysis was done using SPSS 12.0 (SPSS Inc, Chicago, Illinois, United States) statistical software. Comparison between baseline and post-treatment parameters within treatment groups was done using paired *t* test. Comparison of mean percentage change from baseline after 16 wk of therapy between two treatment groups was done using Fisher's exact test. *P* values were two-sided and were considered significant at < 0.05.

RESULTS

At baseline (Table 1), the antireflux therapy and placebo groups were matched with no significant difference between various parameters like age, sex, body mass index, asthma symptoms, reflux symptoms, rescue medication use, FEV₁ and FVC. There was no significant difference in medication compliance between antireflux therapy and placebo groups based on pill counts (95.2% ± 7.4% *vs* 96.7% ± 6.3%, *P* = 0.87).

There was 17.4% reduction in the daytime asthma symptom score (*P* = 0.0002), 19.6% reduction in nighttime asthma symptom score (*P* = 0.0007) and 8.7% reduction

Table 1 16-wk primary and secondary outcome measures of antireflux therapy (mean $\pm$ SD)

Variable	Baseline		16 wk therapy	
	Antireflux therapy	Placebo	Antireflux therapy	Placebo
Age, yr	51.49 $\pm$ 9.83	51.48 $\pm$ 9.79		
Sex, % Male	68.7	68.7		
Female	31.3	31.3		
BMI, kg/m ²	27.33 $\pm$ 1.93	27.37 $\pm$ 1.96		
Asthma symptom score				
Daytime	2.48 $\pm$ 0.80	2.46 $\pm$ 0.79	2.04 $\pm$ 0.68 ^b	2.24 (0.64)
Nighttime	2.60 $\pm$ 0.80	2.59 $\pm$ 0.79	2.09 $\pm$ 0.67 ^b	2.45 (0.71)
Reflux symptom score	2.48 $\pm$ 0.76	2.49 $\pm$ 0.73	1.52 $\pm$ 0.52 ^b	2.45 (0.64)
Albuterol use, number of puffs/week	3.27 $\pm$ 1.04	3.25 $\pm$ 1.02	2.51 $\pm$ 0.69 ^b	3.15 (0.97)
PEFR, L/min				
Morning	283.58 $\pm$ 43.27	285.45 $\pm$ 44.27	306.36 $\pm$ 42.19 ^b	286.01 (43.89)
Evening	283.69 $\pm$ 54.49	288.06 $\pm$ 57.38	311.45 $\pm$ 50.85 ^b	286.63 (53.39)
FEV1				
L	1.89 $\pm$ 0.40	1.85 $\pm$ 0.40	2.10 $\pm$ 0.34 ^b	1.92 (0.41)
% predicted	68.58 $\pm$ 3.56	68.69 $\pm$ 3.59	70.66 $\pm$ 3.02 ^b	68.89 (3.57)
FVC				
L	1.94 $\pm$ 0.37	1.97 $\pm$ 0.35	2.12 $\pm$ 0.31 ^b	1.94 (0.37)
% predicted	69.24 $\pm$ 3.39	69.65 $\pm$ 3.45	71.12 $\pm$ 2.88 ^b	69.28 (3.42)

^b $P < 0.01$ vs Baseline, BMI: Body mass index; PEFR: Peak expiratory flow rate; FEV1: Forced vital capacity in 1 s; FVC: Forced vital capacity.

in reflux symptom score after antireflux therapy compared to baseline ($P = 0.0001$). Antireflux therapy resulted in 23.2% reduction in rescue medication use ($P = 0.0001$), 7.9% improvement in morning PEFR ($P = 0.005$), 9.8% improvement in evening PEFR ($P = 0.003$), 11.1% improvement in FEV₁ (L) ($P = 0.001$) and 9.3% improvement in FVC (L) compared to baseline ($P = 0.002$).

Comparison of mean change from baseline between antireflux therapy and placebo groups revealed significant reduction in daytime asthma symptom score (17.4% vs 8.94%, $P = 0.0001$), nighttime asthma symptom score (19.6% vs 5.4%, $P = 0.0001$), reflux symptom score (8.7% vs 1.6%, $P = 0.0003$) and rescue medication use (23.2% vs 3.08%, $P = 0.0001$) after antireflux therapy compared to mean change in placebo group. There was significant improvement in morning PEFR (7.9% vs 0.2%, $P = 0.004$), evening PEFR (9.8% vs 0.5%, $P = 0.002$), FEV₁ in L (11.1% vs 3.78%, $P = 0.0013$) and FVC in L (9.3% vs 1.52%, $P = 0.0023$) in the antireflux therapy group compared to placebo on comparing the mean change from baseline after 16 wk. These results are demonstrated in Table 1. Improvement in primary and secondary outcome measures was seen in all 99 patients treated with antireflux therapy.

Maintenance medication and adverse events

All patients were treated with one inhalation of salmetrol 50 μ g and fluticasone propionate 250 μ g taken two times everyday at 8:00 and 20:00 (Seretide; Glaxo Smithkline Pharmaceuticals Limited, Mumbai, India). There was no significant difference in the maintenance medication dose between two treatment groups at baseline. There was no change in the maintenance medication during the treatment period in two treatment groups.

There was no significant difference in treatment-emergent adverse events between antireflux therapy and placebo groups over 16 wk of treatment (64% vs 60%, $P =$

0.7). The percentages of severe adverse events were similar in the two treatment groups (10% vs 8%, $P = 0.4$). The severe adverse events included myalgia (4%), aggression (3%), thrombocytopenia (1%), urticaria (1%) and Steven-Johnson syndrome (1%) in the antireflux therapy group.

DISCUSSION

This study shows a significant improvement in daytime and nocturnal asthma symptoms, reflux symptoms, daytime and nighttime PEFR, FEV₁ and FVC after omeprazole and domperidone therapy for 16 wk compared to placebo. This is the second study in medical literature investigating the effect of combined therapy with a proton-pump inhibitor and prokinetic agent in asthmatics. In an earlier study, Jiang *et al*^[19] used Ome 20 mg once daily and Dom 10 mg thrice daily for 6 wk in 30 asthmatics. They found significant improvement in VC, VC%, FVC, FVC%, FEV₁, FEV₁%, PEF, PEF% and bronchial hyper-responsiveness as measured by histamine bronchoprovocation test.

Results of past studies investigating the effect of proton-pump inhibitor therapy on asthma outcome have shown variable results. Some recent studies using different proton pump inhibitors in asthmatics include those by Calabrese *et al*^[20] using pantoprazole 80 mg daily in 34 asthmatics for 6 mo (25 patients had a complete recovery of esophagitis and reflux symptoms and 27 patients had normalization of FEV₁), Kiljander *et al*^[21] using esomeprazole 40 mg twice daily for 16 wk in 350 asthmatics with GERD and nocturnal respiratory symptoms (significant improvement in morning and evening PEFR), Littner *et al*^[22] using lansoprazole 30 mg twice daily for 24 wk in 207 asthmatics with acid reflux symptoms (reduction in asthma exacerbations and improved asthma quality of life, but no improvement in

asthma symptoms or pulmonary function), Gopal *et al*^[23] using Ome 20 mg daily for 4 wk in 70 asthmatics with significant reflux (significant improvement in asthma symptom scores and pulmonary function), and Eryuksel *et al*^[24] using pantoprazole 40 mg daily for 3 mo in 28 asthmatics with laryngopharyngeal reflux as shown by indirect videolaryngoscopy (significant reduction in asthma and laryngopharyngeal reflux symptoms). On reviewing the combined results of 12 studies examining medical therapy in 326 treated asthmatics with GERD in a meta-analysis, asthma symptoms improved in 69%, medication use was reduced in 62%, and evening PEF rates improved in 26% of patients; however, pulmonary function did not improve^[25]. A recent Cochrane Database review examined 12 randomized controlled trials studying antireflux therapy in asthmatics and noted no overall improvement in asthma after GERD therapy^[31]. However, they concluded that subgroups of patients may benefit and pointed out the importance of examining predictors of asthma response.

The role of non-acid reflux in asthmatics who do not respond to proton-pump inhibitor therapy has been described^[32]. We speculate that a sub-group of asthmatics may have increased bronchial responsiveness on exposure to non-acid reflux including bile acids, bile salts and pancreatic enzymes. Combined therapy with a proton pump inhibitor and prokinetic agent may help asthmatics with gastroesophageal reflux by reducing acid as well as non-acid reflux. A new technique, esophageal impedance monitoring makes it possible to detect non-acid reflux and may provide future directions to exploring the relationship between non-acid reflux and asthma. A large on-going trial is exploring the prevalence of acid and non-acid GERD in moderate to severe asthma children aged 1-18 years referred for gastrointestinal evaluation^[33].

We used Dom, a prokinetic agent in addition to omeprazole to treat GERD in our study. Prokinetics have been shown to have a definite role in the treatment of gastroesophageal reflux disease. In short term treatment of gastro-esophageal reflux disease, cisapride (10 mg four times a day or 20 mg twice daily) has proved more effective than placebo and nearly as effective as H₂ blockers in relieving symptoms and healing esophagitis^[34]. Cisapride (10 mg twice daily or 20 mg at bedtime) also prevents relapses in patients with mild esophagitis^[35]. Studies using metoclopramide also showed an improvement in reflux symptoms compared to placebo using metoclopramide 10 mg four times a day^[36]. Domperidone, the prokinetic agent used in our study, is a dopamine antagonist, which does not cross the blood-brain barrier and thus has a better safety profile, with no significant CNS side effects and only a minor incidence of gynecomastia and galactorrhea. Domperidone acts by increasing lower esophageal sphincter tone and by enhancing upper gastrointestinal separately, acting on one of the pathophysiological mechanisms of GERD. It antagonizes the inhibitory effect of dopamine, resulting in stimulation of gastric muscle contraction. This provides a mechanism for the gastrokinetic effect of domperidone^[37]. In a randomized, double-blind, controlled trial conducted in pediatric population, Dom caused a significant reduction in

vomiting compared to metoclopramide and placebo^[38]. A study comparing different maintenance therapies for reflux esophagitis has concluded that addition of prokinetic with antisecretory agent decreases relapse (relapse rate 20% with Ome and only 11% with combination of Ome and cisapride)^[39]. However, Sekiguchi *et al*^[40] found that cisapride often actually exacerbated acid reflux in another study. The use of combination therapy with omeprazole and domperidone should be monitored closely in asthmatics.

In conclusion, our data suggests that combined therapy with Ome and Dom for 16 wk in asthmatics with GERD may be beneficial by reducing asthma symptoms and rescue medication use, and improving pulmonary function.

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