

Gastroesophageal Reflux Disease in Bronchial Asthma and the Response to Omeprazole

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SUMMARY The objective of this study was to determine the incidence of gastroesophageal reflux disease (GERD) in bronchial asthma and the role of omeprazole for asthmatics with symptoms of GERD. Seventy asthmatics were screened for GERD by questionnaire. Patients with a history suggestive of GERD were confirmed by Bernstein test and further investigated for airway responsiveness to instillation of HCl in the esophagus. Symptom score, drug score and spirometric values were recorded initially and after four weeks of treatment with omeprazole. It was found that 74.28% of asthmatics had a history of GERD. Forty patients tested positive by Bernstein test and also showed airway responsiveness to instillation of HCl in the esophagus. There was a significant improvement in symptom scores ($p < 0.001$), drug scores ($p < 0.001$) and spirometric values ($p < 0.001$) after adding omeprazole to their treatment regimen. It was concluded that bronchial asthma and GERD are associated in the majority of patients (57.14%) and such patients are likely to improve with omeprazole.

Bronchial asthma is a complex disease and the list of aggravating factors keeps increasing. The association of gastroesophageal reflux (GER) with a wide variety of pulmonary disorders was recognized as early as 1887.^{1,2,3} Mendelson⁴ described pulmonary aspirations producing an acute asthma-like syndrome with wheezing in some patients. Researchers have suggested that GER is one of the etiologic factors in the development of pulmonary disorders⁵⁻⁷ as well as an aggravating factor for the symptoms of asthma.⁸⁻¹⁰

In children who present with respiratory symptoms as chief complaint or with recurrent episodes of nocturnal cough or wheezing,¹¹ gastroesophageal reflux disease (GERD) has been implicated as the main culprit. To the best of our knowledge only one study from India¹² reported the GERD prevalence of asthmatic children, which was around

39%. In adult asthmatics the incidence of GERD reportedly ranges from 34% to 89%.¹³⁻¹⁶

GER is very common in asthmatics but is often not recognized. A multitude of tests has been used to diagnose GER in asthmatics including barium studies, radionucleoide scintiscanning, pH monitoring and acid perfusion test. Though pH monitoring is considered the gold standard, the acid perfusion test has been widely used based on the clinical onset of symptoms or on a fall in FEV₁ of more than 20% after a positive challenge.¹⁷ Various studies have demonstrated the changes in response to acid instillation in the esophagus and established the relationship

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between GER and bronchial asthma.¹⁸⁻²³ The benefit that asthmatic patients gain from therapy designed to reduce GER provides further support to the relationship between GER and bronchial asthma.²⁴ Proton pump inhibitors such as omeprazole have proved to be very effective in the management of GERD.^{25,26}

The present study was carried out to determine the association of GER with cases of bronchial asthma, to establish the effect of GER on symptoms and spirometric values in asthma as well as to observe the reversibility of the symptoms of asthma and the spirometric values after addition of omeprazole to the existing treatment for asthma.

MATERIALS AND METHODS

The study was conducted at the outpatient department (OPD) of the Department of Respiratory Medicine, Vallabhbai Patel Chest Institute, Delhi. Patients with breathlessness and/or wheezing in the age group of 12-50 years of either sex were included in the study. Smokers, pregnant and lactating women and patients with other respiratory or systemic illnesses were excluded from the study.

The diagnosis of GERD was suspected on the basis of a questionnaire using the criteria described by Field *et al.*²⁶ which emphasized a definitive presence of the following 2 symptoms: heart-burn defined as burning sensation, pain and discomfort in the chest after meals or when lying down; and regurgitation, return of gastric/stomach acid contents in the mouth.

A thorough clinical examination and spirometry (FVC, FEV₁, FEV₁/FVC) were done. Those having a history suggestive of GERD on the basis of the questionnaire were subjected to a Bernstein test (Acid Perfusion Test) to evaluate the presence of GERD. The patient was seated in an upright position and a nasogastric tube was placed 30 cm from the nares. Normal saline was instilled for 15 minutes followed by 0.1 N HCl for 30 minutes or till the symptoms occurred, at the rate of 6 ml/minute (100 drops per minute) through the nasogastric tube. The test was considered positive only if symptoms of heart-burn occurred within 30 minutes of acid perfusion.

Spirometry was done before and after the test and a fall in FEV₁ of more than 20%²⁷ was con-

sidered to be positive for airway response to acid instillation in the esophagus. All the patients were asked to attend the outpatient department regularly to control compliance and optimize treatment for one month prior to including them in the study. All the patients received inhaled steroids and other medications as indicated for each individual patient.

A run-in period of four weeks was carried out. The patients were asked to keep daily symptom and drug intake records and to maintain the chart for a total of 4 weeks. Spirometry, symptom score and drug score were assessed at 2 and 4 weeks.

During the study period of 4 weeks all the cases were orally given omeprazole 20 mg once daily along with the medications for asthma. A symptomatic evaluation, drug intake and spirometry were repeated at 2 and 4 weeks. The results were compared with the values during the run-in period.

The assessment was made on the basis of the symptom score, drug score and spirometry values. Respiratory symptoms included cough, breathlessness/wheeze and sputum, all of which were graded from 0-4 depending on severity. The individual scores were added to these scores to give the total respiratory symptom score. Similarly the total gastric symptom score was obtained from the symptoms of heart-burn and regurgitation which were each graded from 0-3. The total drug score was obtained in a similar way. Various drugs that were given to the patients included inhaled steroids, inhaled salmeterol, inhaled salbutamol (as required), oral theophyllin, oral salbutamol and oral/injectable steroids, which were each graded from 0-4. Details are given in the appendix. The statistical analysis was done using the mean value of the run-in period as the baseline.

RESULTS

Seventy asthmatics were screened by questionnaire for an association of symptoms of GER. Fifty-two (74.28%) patients gave a history suggestive of GER. All 52 patients were subjected to a Bernstein test with spirometry before and after the test. Forty patients showed a positive Bernstein test and a fall in FEV₁ > 20%.

Table 1 shows the symptoms seen in these 40 patients with confirmed GERD. There were 22

males and 18 females. The age varied between 16 to 40 years. All of them had perennial asthmatic problems. The severity of asthma is given in Table 2. A family history of asthma was present in 20% and a family history of GERD was present in 28%. The results of the spirometry before and after the Bernstein test are shown in Table 3. The prevalence of GERD in bronchial asthma was 57.14%. All 40 patients were given 20 mg of omeprazole daily for 4 weeks. There was a significant improvement in symptom scores, drug scores, and spirometric values (Table 4). It is interesting to note that there was a consistent improvement in both gastric and respiratory symptoms since the start of the therapy.

DISCUSSION

In the present study 52 (74.28%) patients with bronchial asthma had symptoms suggestive of GERD. The incidence of GERD in asthmatics has been reported ranging from 34-89%.¹³⁻¹⁵

We submitted these patients to a Bernstein test followed by spirometry to look for a change in FEV₁ after acid instillation. We found that 57.14% asthmatics had a positive Bernstein test. There are other reports^{28,29} with similar results. In our study we have seen a significant fall in FEV₁ of more than 20% on acid instillation. We also found a significant fall in FVC in addition to a fall in FEV₁ in response to acid instillation in the esophagus.

In the present study the treatment with omeprazole has improved asthma symptoms and pulmonary function in asthmatics having associated gastroesophageal reflux disease. All the 40 (100%) asthmatic patients with symptoms of GERD and positive Bernstein test showed a significant clinical improvement of their symptoms of asthma and their pulmonary functions under omeprazole therapy.

This improvement has also been reported by others.^{10,30-33}

Harding *et al.*³⁴ have shown that asthma symptoms and pulmonary functions improved in 73% of the asthmatics after treatment with omepra-

Table 1 Symptoms of the patients

Breathlessness	N = 40
Nocturnal wheezing	34 (85%)
Associated with drinking tea	32 (80%)
Associated with drinking coffee	24 (60%)
Associated with lying down	28 (70%)
Associated with spice consumption	36 (90%)
GERD	
Presence of heartburn	40 (100%)
Presence of regurgitation	38 (95%)
Presence of symptoms of GERD in association with wheeze/cough	39 (97.5%)
Worsening of cough with symptoms of GERD	39 (97.5%)
Wheezing/shortness of breath with symptoms of GERD	39 (97.5%)
Increased use at the time of GERD	30 (75%)

Table 2 Percentage predicted FEV₁

Percentage predicted FEV ₁	No. of patients
≥ 80%	1
70-80	22
60-70	13
50-60	2
< 50%	2

Table 3 Change in spirometry with Bernstein test

Pre test		Post test		Mean fall in FVC (l)	Mean fall in FEV ₁ (l)	Avg. fall in FEV ₁ (%)
Avg. FVC (l)	Avg. FEV ₁ (l)	Avg. FVC (l)	Avg. FEV ₁ (l)			
2.52 ± 0.80	1.76 ± 0.60	2.20 ± 0.75	1.35 ± 0.46	0.32	0.40	23.05 ± 4.56

Table 4 Symptom scores, drug scores and spirometry values before and after omeprazole

Days	Before omeprazole				After omeprazole		
	0	15	30	Mean Scores	0	15	30
Respiratory symptoms	11.20 ± 1.22	10.42 ± 1.03	10.29 ± 0.82	10.64 ± 0.83	10.30 ± 0.83	6.69 ± 1.01*	3.58 ± 1.26*
Gastric symptoms	4.65 ± 0.66	4.69 ± 0.60	4.70 ± 0.63	4.68 ± 0.61	4.70 ± 0.63	2.72 ± 0.83*	0.35 ± 0.54*
Drug scores	24.15 ± 9.56	26.11 ± 9.66	25.65 ± 9.49	25.30 ± 9.55	25.65 ± 9.49	22.49 ± 9.55*	20.66 ± 8.98*
FVC (l)	2.52 ± 0.79	2.55 ± 0.77	2.57 ± 0.74	2.55 ± 0.76	2.57 ± 0.75	2.82 ± 0.76*	2.94 ± 0.77*
FEV₁ (l)	1.76 ± 0.58	1.76 ± 0.56	1.76 ± 0.55	1.77 ± 0.52	1.78 ± 0.52	2.05 ± 0.58*	2.23 ± 0.62*
FEV₁/FVC	69.05 ± 7.95	68.87 ± 6.68	69.37 ± 5.91	69.37 ± 5.91	69.37 ± 5.91	72.72 ± 5.55*	75.87 ± 4.43*
PEFR (l/m)	274.70 ± 78.87	276.00 ± 75.54	277.50 ± 72.07	277.50 ± 74.37	277.50 ± 72.07	326.00 ± 77.54*	370.70 ± 73.60*

* $p < 0.001$ compared to average values before omeprazole

zole. Meier *et al.*³⁵ showed that only some patients (4 out of 15) showed improvement in asthma symptoms on omeprazole. Teichtahl *et al.*³⁶ showed that omeprazole given in daily doses of 40 mg improved the evening PEFr in asthma patients but showed no improvement in asthma symptoms. Ford *et al.*³⁷ in a similar study concluded that treatment of GER with omeprazole in asthmatics does not improve asthma symptoms or peak expiratory flow rates.

Omeprazole is the most effective medical treatment for esophagitis. The 4 week trial was selected to provide study participants with sufficient therapy. In our study all 40 patients showed improvement in asthma symptom scores in concurrence with gastric symptom scores, and the changes were consistent during the 4 week study period, contrary to the studies by Harper *et al.*³⁸ and Harding *et al.*,³⁴ who showed that asthma improvement lagged behind reflux symptom improvement. Harding *et al.*³⁴ suggested that 3 months of therapy with omeprazole is required and many asthmatics (27%) even required more than a 20 mg daily dose of omeprazole.

The present study was not placebo controlled. However the observations strongly suggest that the response of omeprazole in our study was not merely that of a placebo. Our study showed a response in 100% of the individuals which is strikingly

higher than any of the placebo responses reported so far. Our study compares well with another non placebo trial by Harding *et al.*³⁴ in which the response rate was 73%. Thus although ours was not a placebo controlled trial, to the best of our knowledge it was the largest trial for the role of omeprazole in asthmatic patients with GERD and shows that such patients are likely to improve with antireflux therapy.

We conclude that asthmatics should be screened for the presence of gastroesophageal reflux disease since most of these patients improve significantly through the addition of omeprazole to the standard treatment for asthma.

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APPENDIX

Respiratory symptoms	Score
Cough	
No symptom	0
Morning or late night	1
Late evening	2
Day time also	3
Most of the time	4
Sputum	
Nil	0
Watery	1
White	2
Dirty white	3
Yellow	4
Breathlessness/Wheeze	
Nil	0
Morning or late night	1
Late evening	2
Day time also	3
Most of the time	4
Gastric Symptoms	
Heartburn	
Nil	0
Occasional	1
Frequent (requiring antacids)	2
Interfering with activities	3
Regurgitation	
Nil	0
Occasional	1
Regurgitation occurring on lying down	2
Occurrence of pulmonary aspiration and cough	3
Drug Score	
Salbutamol	
Nil	0
Inhaled salbutamol 200 µg (sos) by inhaler	1
Infrequent oral salbutamol	1
Oral salbutamol 2 mg tds	2
Oral salbutamol 4 mg tds	3
Inhaled salbutamol by nebuliser	4
Salmeterol	
1 puff bid	2
2 puffs bid	4
Steroids	
Inhaled steroids 400 µg/day	1
Inhaled steroids 800 µg/day	2
Inhaled steroids 1,600 µg/day	3
Oral steroids	4
Injectable steroids	5
Theophylline	
Nil	0
Infrequent	1
200 mg bid	2
300 mg bid	3
Injectable	4
Hospitalization	5