Gastroesophageal reflux in the patiens with asthma[1]

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SUMMARY

Thirty one patients with asthma (mean age was 44.4 ± 10.7; range 18-63) were investigated for gastroesophageal reflux (GER). The patients were seperated into two groups according to presence of reflux and/or nocturnal symptoms. 13 patients had one of the reflux and/or nocturnal asthma symptoms (Group 1), whereas 18 patients had none of them (Group 2). To assess GER patients underwent to scintigraphy with Tc^{99m}. GER was determined 4 of 13 patients in group 1 (30,7 %) and 1 of 18 patients in group 2 (5,5 %). There was significant difference between the group 1 and group 2 in that respect ($p < 0,001$). The patients with established GER (5 patients) were given Omeprazole (a proton pomp inhibitor) 40 mg daily for 4 weeks following a 2 week placebo period. The patients recorded their daily and nocturnal symptoms of asthma, additional salbutamol use, morning and evening peak expiratory flow rates (PEFR) measurements in a daily chart during placebo and omeprazole treatment without changing their antiasthma treatment. Their PEFR, FEV_1 values, daily and nocturnal symtoms and additional beta agonist use did not changed after omeprazole treatment except one. But their reflux symtoms (heartburn and regurgitation) were improved. As a consequence, we suggested that asthmatics which have some complaints of reflux should be searched for GER. Not the respiratory functions but GER symptoms can be improved with antireflux treatment.

Key words: Gastroesophageal reflux. Asthma. Omeprazole. Tecnitium scintigraphy.

Allergol et Immunopathol 2001; 29(4): 123-128.

INTRODUCTION

Reflux of fluid and air into and through the esophagus is a normal phenomenon. But acid reflux may cause some problems such as recurrent pneumonia, bronchiectasis and pulmonary fibrosis (1). In addition, gastroesophageal reflux (GER) is expected one of the triggers which cause asthma exacerbations in the asthmatics (2-5). A higher prevalence of GER has been shown in the asthmatics (2, 3, 6, 7) and in the patients with chronic pulmonary symptoms (8). Moreover, in some studies antireflux therapy improved the asthma symptoms and also respiratory functions (4, 9). Although it is difficult to say the exact prevalence of GER in the asthmatics, it ranges from 33 % to 90 % in the adults and from 47 % to 64 % in children (10).

The exact mechanism which causes or exacerbates asthma symptoms has not been established yet. Two different mechanisms have been published according to the results of the previous studies; the first is the activation of vagally mediated reflex from the esophagus to the lung resulting cough and bronchospasm (11, 12) and the second is the inducing a chemical tracheobronchitis by microaspiration of gastric contents into the lung (13, 14). With the above descriptions, it can be though that to detect and treatment of GER could help to improve some symptoms and lung function measures of the asthmatics.

We aimed to demonstrate the prevalance of GER in a group of asthmatic patient using tecnitium scin-

Table I

Characteristics of patients studied

	All patients	Group 1	Group 2
Age, yr (range)	44.4 ± 10.7 (18-63 yr)	48.5 ± 9.3 (18-61)	41.4 ± 10.9 (38-63)
Sex (M/F)	5/26	1/12	4/14
Mean FEV_1 (%)	75.6 ± 22.3 (50-121)	68.5 ± 17.5 (50-106)	80.7 ± 24.3 (50-121)
Duration of asthma, yr (range)	6.9 ± 4.7 (1.5-25)	8.7 ± 6.2 (2.5-25)	5.6 ± 2.7 (1.5-11)
Severity of asthma (severe/moderate/mild)	7/10/14	3/7/3	4/3/11
Reflux symptoms (Yes/No)	13/18		

F: female; yr: year; FEV_1: forced expiratory volume in one second; M: male.

tigraphy, and to demonstrate a measurable improvement in symptoms and respiratory functions by antireflux therapy with omeprazole.

MATERIALS AND METHODS

Thirty one nonsmoker asthmatic patients (5 men and 26 women; mean age was 44.4 ± 10.7 years, range 18-63 yr) were randomly selected regardless of the antiasthma drugs used from the outpatient department with no evidence of current pregnancy. Asthma was diagnosed according to recommendations of American Thoracic Society (15). The characteristics of patients are in table I. Asthma severity was classified according to GINA guidelines in mild persistent, moderate persistent and severe persistent (16). There is no patient who has intermittent asthma. 14 of 31 patients were using inhaled corticosteroid plus short acting beta agonist drug as required, 12 were using inhaled corticosteroid plus long acting beta agonist drug regularly and 3 were inhaled corticosteroid plus long acting beta agonist plus theophylline. 2 patients which were mild intermittent asthmatics were receiving beta agonist as required only.

Patients divided into two groups according to the absence or presence of the reflux and/or nocturnal asthma symptoms. If the patient has one of the reflux symptoms (heartburn and regurgitation) and/or has any of the nocturnal asthma symptoms (night cough, wheezing and shortness of breath) included into group 1 (symptomatic group). If the patient has none of these symtoms included into group 2 (asymptomatic group). Group 1 consisted of 13 patients which have one of the reflux and/or nocturnal symptoms. Group 2 consisted of 18 patients which have none of the symptoms. The characteristics of the patients in group 1 and 2 are in table I.

Gastoesophageal scintigraphy was performed after 4 hr test. The patient was given 1 mC ^{99m}Tc-sulphur colloid in 300 mL orange juice orally. Image was taken in supine position, with coronal plane parallel to the collimator. The study is performed on a large field-of-view gamma camera (GE 400 AC/T) interfaced to a computer. Images were acquired using a 64 × 64 matrices. Fifteen minutes after dose administration sequential 60 second images were obtained for 16 minutes. The pressure on abdominal wall was done by four minutes of intervals at the 4th min, 8th min, 12th min and at the 16th min. All patients gave informed consent.

We give omeprazole (40 mg/day) to the patients who has established GER with scintigraphy for 4 weeks following a 2 week placebo period during which an identical placebo capsule was given. No change in anti asthma medication was allowed during the study. The patients recorded on a dairy chart their day and nighttime asthma symptoms scaled as follows during placebo and treatment period (9):

Day time
0, No symptom.
1, Mild symptom, done daily work well.
2, Moderate symptom, some effect on the daily work.
3, Severe symptom, not done daily work.

Night time
0, No symptom, slept well.
1, Mild symptom but slept well.
2, Woken 2-3 times because of symptoms.
3, Not slept almost all night because of symptoms.

The patients also recorded their peak expiratory flow rate (PEFR) values using a mini Wright peak flow meter between 7:00 and 8:00 AM and between 7:00 and 8:00 PM during placebo and treatment

Table II

Characteristics of 5 patients with established gastroesophageal reflux (GER)

No	Age, sex	Nocturnal symp.	GER symp.	FEV_1 %	Severity of asthma	Asthma duration, yr	Therapy
1	45, F	No	No	73	MP	8	ICS
2	42, F	No	Yes	82	MP	5	ICS
3	45, F	Yes	Yes	52	S	3	ICS + LB + T
4	63, F	Yes	Yes	52	S	9.5	ICS + LB
5	62, F	No	Yes	63	Moderate	6	ICS

F: female; ICS: inhaled corticosteroid; LB: long acting beta agonist; MP: mild persistent; S: severe; symp: symptom; T: theophylline; yr: year.

period daily during placebo and omeprazole treatment. The chart was also used to record the daily use of inhaled salbutamol. FEV_1 was measured using a dry bellows spirometer (Vitalograph, UK). The reflux symptoms were recorded as follows at the time of entry into the placebo and at the end of treatment period (9):

Heartburn
0, No heartburn.
1, Occasional heartburn.
2, Heartburn requiring medical advice and antiacids.
3, Heartburn interferring with physical activities.

Regurgitation
0, No regurgitation.
1, Occasional regurgitation on straining or position change.
2, Predictable regurgitation on straining or position change.
3, Occurrence of pulmonary aspiration.

Statistics

The students paired or unpaired t test for nonparametric data, Mann Whitney U test and Fisher exact Chi-square tests were used for comparing the variables. The results were expressed as mean ± standart deviations (SD). A p value is equal or less than 0.05 was considered as significant.

RESULTS

The characteristics of the patients in each group are in table I. There were no differences between group 1 and 2 in respect to age, duration of asthma symptoms and mean values of FEV_1 ($p > 0.05$).

Of the 31 patients entered into the study, 5 had GER with scintigraphy (16.1 %). Only one patient was from group 2 and all the others were from group 1 (table II). So of all the patients from symptomatic group, 4 had detectible GER with scintigraphy (30.7 %). In nonsymptomatic group it was 5,5 %. There was statistically significant difference between goup 1 and group 2 in regard to established GER ($p < 0.01$).

The mean values of the daytime and nocturnal asthma symptoms, daily rescue salbutamol use, mean percentages of FEV_1 values, morning and evening PEFR values and reflux symptoms (heartburn and regurgitation) of the 5 patients with GER are in table III. As compared with the placebo period, there was no difference in individual measures of FEV_1 in 5 patients with GER ($p > 0.05$). Although there were decreases in mean values of daily salbutamol use, daytime and nocturnal asthma symptoms and improvements in mean values of morning and evening PEFR measurements in the patients, only one patient showed statistically significant improvement in morning PEFR and decrease in rescue salbutamol use after omeprazole (the 3rd patient in table III, $p < 0.05$). Omeprazole diminished reflux symptoms in all except one who had no reflux symptoms but established GER. Omeprazole improved heartburn score with a slight significance ($p = 0,05$) and regurgitation score with nonsignificance ($p = 0,07$).

DISCUSSION

There has been growing concern on asthma coexisting with gastroesophageal reflux (GER) (1-7). Although in some reports antiasthma treatment said to cause GER reducing lower esophageal sphincter (LES) pressure (17) or increasing acid secretion (18), the asthmatics may also show high prevalance of GER regardless of asthma treatment (6). However true prevalance is difficult to determine from the stu-

Table III

Symptom scores, rescue salbutamol use, PEFR measurements, FEV_1 values and reflux symptoms in the patients with GER during placebo and omeprazole period

Patient		1	2	3	4	5
Morning PEFR,	Pl,	337 ± 10.6	377 ± 8.9	227 ± 6.7	219 ± 5.4	275 ± 7.6
	O,	362 ± 16.7	382 ± 7.3	229 ± 24.3#	220 ± 5	272 ± 6.5
Evening PEFR,	Pl,	371 ± 6.8	390 ± 6.7	245 ± 5.3	224 ± 7.8	292 ± 5.9
	O,	369 ± 10.8	392 ± 9.5	239 ± 7	228 ± 8.8	276 ± 5.7
Nocturnal sym.,	Pl,	0.06 ± 0.2	0.4 ± 0.5	0.9 ± 0.6	0.9 ± 0.6	0.7 ± 0.5
	O,	0.06 ± 0.2	0.3 ± 0.5	0.4 ± 0.5	0.7 ± 0.6	0.4 ± 0.5
Daytime sym.,	Pl,	0.8 ± 0.6	0.6 ± 0.5	1.3 ± 0.7	1.3 ± 0.7	1.0 ± 0.5
	O,	0.7 ± 0.6	0.4 ± 0.5	1.1 ± 0.5	1.1 ± 0.5	0.9 ± 0.6
Salbutamol use,	Pl,	1 ± 0.7	0.3 ± 0.5	1.6 ± 0.5	1.3 ± 0.5	1.2 ± 0.6
	O,	0.8 ± 0.7	0.4 ± 0.5	1.1 ± 0.7#	0.8 ± 0.6	0.9 ± 0.4
FEV_1, %	Pl,	75	85	50	54	65
	O,	74	83	53	52	64
Heartburn,	Pl,	0	2	1	2	2
	O,	0	0	0	0	1
Regurgitation	Pl,	0	1	1	2	1
	O,	0	0	0	1	0

FEV_1: forced expiratory volume in one second; O: omeprazole; PEFR: peak expiratory flow rate; Pl: placebo; sym: symptom.
#: $p < 0.05$ (There is statistically significant improvement in morning PEFR and decrease in salbutamol use after omeprazole).

dies published. It ranges from 33% to 90% in the adult patients and according to the diagnostic procedure used. We found in all randomly choosen asthmatic group a prevalance of GER was 16.7%. That seems to be lower than some previous studies. We think that it could be higher if we had choosen symptomatic patients. But, in our symptomatic group the prevalance (30.7%) was quite different from nonsymptomatic group (5.5%). Although nocturnal asthma symptoms are expected findings in the asthmatics, we know that they are found in a greater incidence in the asthmatics with GER. So, we have shought nocturnal asthma symptoms in addition to reflux symptoms to investigate GER. We found GER in one patient from nonsymptomatic group. Perhaps this finding could be explained by perception differences of patients on the symptoms. In addition we have not established GER with scintigraphy in those patients complaining from some GER symptoms.

Various mechanisms by which gastroesophageal reflux may trigger bronchospasm have been suggested such as aspiration of acid material to the bronchial tree (13, 14) or a reflex mechanism caused by acid irritation of the esophageal mucosa (11, 12). It has not been established well yet. Some studies showed that acidification of the esophageal mucosa causes bronchial obstruction (5, 11) and some others did not (20, 21). Davies and associates also showed bronchoconstriction caused by esophageal acidification but only in the patients with positive response to the esophageal acid infusion (Bernstein) test (22). And the authors suggested that a GER induced exacerbation of asthma is related to the several factors, such as reflux of gastric acid into the esophagus, an acid sensitive esophagus (positive Bernstein test response) and a low nocturnal threshold to bronchoconstrictive stimuli. If so, we can explain why GER has been established in one of our patients in spite of the awareness of symptoms. Certainly there are a lot of factors could change the results such as age, use of cigarette and alcohol consumption effecting LES pressure. Our patients were not smokers and alcohol users, and there was not a statistical difference in the ages between group 1 and 2. Moreover, in a previous study, age has not been accepted as a predictor for GER in the asthmatics (7).

Another point of the present study is that, a clear significance on the occurrence of GER in severe asthmatics than those with mild ones ($p < 0.01$). 7 of 31 asthmatics had severe asthma and 2 of them had established GER. Although being in small numbers, that result can be consistent with the theory of severe asthma or intense asthma medication could be a cause of GER. The interaction of asthma and GER can be thought as two sided. That means as well as GER can be a cause of asthma, asthma can also be a cause of GER. Alterations in lung mechanics, such as hyperinflation and flattening of the

diaphram may be a cause for inducing GER (23). Antiasthma medications are also said to cause of GER reducing the LES pressure (24, 25), although there is evidence opposite to it (7). So, GER and asthma may be associated but it is hard to establish which one is the primary abnormality. We think that complaints of patients, although being subjective can give some clues of discrimination. Our patients (numbers 3, 4 and 5 in table II) gave a history of GER symptoms begin after asthma diagnose. If changes in lung mechanics be a cause of GER it can be though that severe asthmatics would be suspectible for GER rather than mild ones. And those patients should be followed in that respect also. Cause there are small numbers of patients in our study group and the patients history is a rather subjective data it is hard to say that asthma is a cause of GER in the patients.

Whatever the cause, some of the studies showed improvement in symptoms and also in lung functions with antireflux treatment in asthmatic patients (4, 9). In most of the studies H-2 receptor blockers were used in the treatment of GER and there are different results. Some showed an improvement only in the symptoms with H-2 blockers (9, 26). In one study, pulmonary functions also improved with cimetidine (27). Omeprazole is a relatively new drug in this era and known as a proton pump inhibitor in gastric parietal cells. There are not more studies with omeprazole in the asthmatics with GER. The first report is a case with GER whose asthma symptoms were improved after omeprazole (28). In a study with omeprazole an improvement was shown in FEV_1 values of the patients (29), whereas in another no improvement in both symptoms and pulmonary functions were shown (30). These conflicting results may be originating from the different numbers and characteristics of patients studied and from the methods used. We also have small numbers of patients with established GER. We compared the individual values of each patient during placebo and omeprazole period. 4 patients showed a subjective improvement in reflux symptoms but only one patient (patient 3) showed an improvement in morning PEFR as well as a decrease in additional salbutamol use. It is hard to estimate which patients can experience respiratory improvement when GER is treated. Asthma is a chronic disease in which not only GER plays a role but a lot of intrinsic and extrinsic factors. But we could say that, in those patients which have gastroenterologic complaints and/or nocturnal asthma symptoms in spite of antiasthma therapy GER should be searched, particularly in those patients whose reflux symptoms begin after asthma diagnosis. Antireflux treatment may have some benefit on reflux and pulmonary symptoms of some patients also as stated before (30).

RESUMEN

En 31 pacientes (media de edad: 44,5 ± 10,7 años) se investigó la posible existencia de reflujo gastroesofágico (RGE). Los pacientes se separaron en dos grupos, de acuerdo con la presencia de síntomas de reflujo y/o síntomas nocturnos. 13 pacientes tenían uno de los síntomas de reflujo y/o de asma nocturna (Grupo 1) mientras que los otros 18 no tenían ningún síntoma (Grupo 2). Para valorar el RGE se efectuó estudio mediante escintigrafía con ^{99m}Tc. Se encontró RGE en 4 de los 13 pacientes del grupo 1 (30,7%) y en 1 de los 18 del grupo 2 (5,5%). En este respecto, hubo diferencia significativa entre ambos grupos ($p < 0,001$). A los 5 pacientes con RGE establecido se les administró omeprazol (un inhibidor de la bomba de protones), 40 mg/día durante 4 semanas, seguidas de otras 2 semanas con placebo. Los pacientes anotaron los síntomas diurnos y nocturnos de asma, el consumo de salbutamol, el valor del PEF de la mañana y la noche, mientras tomaron omeprazol o placebo, sin haber cambiado el tratamiento del asma. Ninguno de estos parámetros se modificó al tomar omeprazol, salvo en uno de los pacientes. Sin embargo, mejoraron los síntomas de reflujo (acidez y regurgitación). Como consecuencia, sugerimos que a los asmáticos que tienen algunos signos de reflujo se les debería investigar un posible RGE. Con el tratamiento anti-reflujo, pueden mejorar los síntomas de RGE pero no los respiratorios.

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Palabras clave: Reflujo gastroesofágico. Asma. Omeprazol. Escintigrafía con tecnecio. Gammagrafía con tecnecio. ^{99m}Tc.

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