Original Article

Evaluation of pantoprazol treatment response of patients with asthma and gastroesophageal reflux: a randomized prospective double-blind placebo-controlled study*

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Abstract

Objectives: To determine the effect that the treatment of GERD has on the clinical management, as well as the respiratory function, of patients with asthma and to evaluate the clinical characteristics of this group of patients. **Methods:** Patients with asthma and concomitant GERD, documented using 24-h pH-metry, were evaluated by means of quality of life questionnaires, as well as questionnaires related to respiratory and digestive symptoms. In addition, esophageal manometry, spirometry and the determination of peak expiratory flow were also performed prior to and after the study. Forty-nine individuals who were diagnosed with GERD by means of 24-h esophageal pH-metry were selected and participated in a clinical randomized double-blind placebo-controlled study, involving the administration of 40 mg/day of pantoprazol for 12 consecutive weeks. **Results:** Forty-four individuals completed the study (n = 22 per group). There was significant improvement in the scores for respiratory symptoms and quality of life only in the group that received pantoprazol (p = 0.01 and p = 0.001, respectively). No respiratory function parameters changed in either group. **Conclusions:** In this study, the effective treatment of GERD improved patient quality of life, and the symptoms of asthma significantly decreased in the group that received the medication. There were no changes in pulmonary function parameters.

Keywords: Asthma; Gastroesophageal reflux/treatment; Diagnosis; Antacids.

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Introduction

The prevalence of diseases jointly affecting the respiratory and digestive systems is high.[1] It is estimated that asthma affects 10% of the adult population.[2] However, in epidemiologic studies, occasional heartburn has been reported by up to 58% of adults, whereas daily heartburn affects up to 7%.[3] In recent decades, the number of studies associating gastroesophageal reflux disease (GERD) with respiratory and otorhinolaryngologic manifestations has increased.[4-7] Well-documented physiopathological mechanisms have been described, helping to explain how these diseases interact. Studies in animals[8,9] and in humans[10,11] have shown that GERD can aggravate asthma by means of microaspiration, vagal reflex, and increased airway responsiveness. Therefore, drug and surgical anti-reflux therapies should both improve, or eventually resolve, the respiratory symptoms of some patients. However, in two meta-analyses, published in 1998[11] and in 2000,[12] in which studies on anti-reflux therapy in patients with asthma were compiled, it was shown that the objective improvement in respiratory symptoms of patients was followed by only discrete or no detectable improvement in the pulmonary function of those patients. In another systematic review, it was concluded that GERD treatment resulted in no consistent benefit for patients with asthma.[13] The role of GERD as an aggravating factor for asthma is still controversial, despite the well-known association between these diseases. The same is true regarding the treatment of reflux in patients with asthma.

The objective of the present, prospective study was to systematically investigate the clinical and functional response, as well as the quality of life, in patients with asthma and concomitant GERD submitted to anti-reflux therapy using pharmacological acid ablation with a proton pump inhibitor (pantoprazol, 40 mg/day for three consecutive months).

Method

A randomized prospective double-blind placebo-controlled study, with a 90-day follow-up period, was conducted. The Ethics in Research Committee of the *Santa Casa de Porto Alegre* Hospital approved the study design. The initial inclusion criteria were being older than 18 years of age, having been clinically/functionally diagnosed with asthma, and having concomitant GERD. In addition, only patients presenting a clinical history consistent with asthma and symptoms stabilized for at least two months were included. Furthermore, spirometry results had to be characteristic: forced expiratory volume in one second/forced vital capacity ratio (FEV_1/FVC) < 90% of predicted, indicating airflow obstruction; and obstruction reversibility represented by FEV_1 > 200 mL and 7% of predicted. Moreover, patients presenting positivity for bronchial hyperresponsiveness on the methacholine bronchoprovocation test were included, regardless of the spirometry findings. The differentiation between a diagnosis of symptomatic GERD and one of asymptomatic GERD was made using stationary esophageal manometry followed by 24-h esophageal pH-metry. Exclusion criteria were as follows: recent history of smoking (past eight weeks); abnormalities in sinus/chest X-rays; history of proton pump inhibitor use within four weeks preceding the study outset; history of H-2 receptor blocker use within two weeks preceding the study outset; systemic arterial hypertension when using angiotensin-converting enzyme inhibitors, β-adrenergic receptor blockers, or calcium channel blockers that could not be changed; presence of other severe systemic diseases; pregnancy; illiteracy of a complete lack of understanding of the forms that had to be completed.

Pulmonary function tests were carried out using a KOKO® flow spirometry (Pulmonary Data Service Instrumentation, Inc., Louisville, KY, USA). These tests were performed in accordance with the Pulmonary Function Test Guidelines established by the Brazilian Thoracic Society.[14]

Esophageal manometry was carried out with a perforated six-pressure-channel catheter (Synectics, Stockholm, Sweden), with three distal radial and three proximal channels 5 cm apart.

The perforated catheter carried a capillary pneumohydraulic pump (Mui Scientific, Mississauga, Ontario, Canada) and pressure was analyzed with a digital polygraph (Polygraph®; Synectics) with real-time pressure readings (Polygram®; Synectics). Immediately after esophageal manometry, a pH-metry catheter with a semi-disposable distal antimony electrode (Synectics) was introduced through the nose and positioned at 5 cm above the upper limit of the inferior esophageal sphincter,

which had been previously located by manometry. The electrode was connected to a portable detector (Mk III; Synectics) and remained connected for 24 h. After the pH-metry catheter was removed, the data were transferred to the analysis software program (Esophogram®; Synectics). The parameters in study and the score adopted were those devised by Johnson & DeMeester,[15] whose description of normal values is shown in Table 1.

The selected patients underwent pretreatment, in which they performed peak expiratory flow (PEF) maneuvers using a Mini-Wright® meter (Clement Clarke International Limited, Essex, UK), every day, in the morning and in the evening, for 10 consecutive days. The patients also completed a daily diary on asthma and GERD symptoms for 10 consecutive days. This diary was based on the symptoms diary developed by Harding *et al.*,[16] shown in Table 1. During this same phase, the technique previously used for inhaled medication, as well as treatment compliance, were reviewed.

Table 1 - Demographic, clinical and functional characteristics of patients at the study outset.

Variable	Placebo		Medication		p
	n	%	n	%	
Age (years)	45 ± 12	-	40 ± 12	-	0.15
Males	2	9.1	7	36.4	0.007
Use of long-acting β_2-agonists	14	64	10	45	0.36
Use of oral corticoids	4	18	2	9	0.66
GERD symptoms score*	12.9 ± 9	-	11.4 ± 7	-	0.56
pH-metry					
-DeMeester score (normal 14.7)	40.1 ± 28	-	29.7 ± 12	0.12	0.12
-% total time (normal < 4.2%)	9.5 ± 7	-	7.5 ± 3	0.25	0.25
-% time standing (normal 6.3%)	8.3 ± 7	-	7.2 ± 5	0.58	0.58
-% time supine (normal < 1.2%)	11.7 ± 14	-	7.7 ± 8	0.23	0.23
-Episodes > 5 min (normal < 3)	4.7 ± 4	-	3 ± 2	0.16	0.16
-Number of reflux episodes (normal < 50)	115.9 ± 59	-	94 ± 37	0.12	0.12
Manometry*					
-LES tonus (normal 14-40 mmHg)	15.5 ± 5	-	18.1 ± 5	0.06	0.06
-LES extension	5 ± 1	-	5.5 ± 1	0.16	0.16
-UES tonus	67.6 ± 32	-	63.4 ± 31	0.65	0.65
Asthma, nocturnal SS*	66 ± 26	-	67 ± 27	-	0.91
Asthma, diurnal SS*	68.8 ± 26	-	68.4 ± 29	-	0.96
QoL*					
-Total	63.8 ± 13	-	61.6 ± 15	0.63	0.91
-Physical limitation	60 ± 20	-	63.7 ± 15	0.59	0.96
-Symptoms	47.3 ± 23	-	55.4 ± 26	0.42	0.63
-Compliance	47.8 ± 26	-	53.6 ± 24	0.45	0.59
-Socioeconomic	61.3 ± 19	-	60.4 ± 20	0.87	0.42
-Psychosocial	56 ± 13	-	58 ± 22	0.77	0.45
Diurnal PEF*	264 ± 86	-	317 ± 13	-	0.11
Nocturnal PEF*	261 ± 83	-	307 ± 12	-	0.14
FVC (% predicted)*	85.8 ± 15	-	79.5 ± 17	-	0.20
FEV_1 (% predicted)*	60.4 ± 19	-	61.6 ± 19	-	0.83
FEV_1/FVC (% predicted)*	69.4 ± 13	-	71.7 ± 11	-	0.53

LES: lower esophageal sphincter; UES: upper esophageal sphincter; SS: symptoms score; PEF: peak expiratory flow; FVC: forced vital capacity; FEV_1: forced expiratory volume in one second; QoL: quality of life score (points); and *mean ± standard deviation.

At the end of the pretreatment phase, patients completed the asthma quality of life questionnaire developed jointly by the Federal University of São Paulo and the Paulista School of Medicine,[16,17] which was adapted and validated for use with the Brazilian population based on the domains investigated by Juniper and Guyatt.[18] After the questionnaires had been completed, the intervention began. The patients were randomly distributed into two treatment groups. The patient in one of the groups received pantoprazol (40 mg in a single daily dose), and those in the other group received a placebo. Examiners and patients were both blinded as to the medication being used by any given patient. All subjects were assessed every month by means of a medical visit questionnaire to determine treatment compliance and possible side effects. During the last week of the study, patients were again submitted to a control 24-h pH-metry. In the final medical visit, patients again completed the quality of life questionnaire and performed the PEF maneuvers, as well as being submitted to pulmonary function tests by means of spirometry. The 10-day symptoms diaries were then collected.

Data were compiled in a spreadsheet (Microsoft Office Excel®), and analyses were carried out using the SPSS statistical software program, version 10 (SPSS Inc., Chicago, IL, USA). Demographic, clinical and laboratory variables for both groups were evaluated for normal distribution and are expressed as means ± standard deviations. In order to evaluate differences between the pretreatment and posttreatment phases for each group in terms of pH-metry, symptoms scores and quality of life, the Wilcoxon rank sum test was used. The Mann-Whitney test was used to compare variables between the two groups prior to and after treatment. Comparisons between morning and evening PEF, as well as spirometry values between treatment and placebo groups, were carried out using the unpaired Student's t-test. For intragroup comparisons prior to and after the study, we used paired Student's t-test. For all statistical tests, the level of significance was set at 5% ($p < 0.05$).

Results

Of the 73 patients with asthma that met the initial inclusion criteria of the study, 49 were diagnosed with GERD and were eligible for the study. Of those, 5 were excluded: 2 due to worsening of symptoms and consequent hospitalization; 1 due to noncompliance with the protocol; 1 due to intolerance to the medication used in the study; and 1 due to having started smoking. Therefore, the study sample consisted of 44 patients at the study outset. Of those 44, 9 were not submitted to the final pH-metry, and therefore only 35 completed the protocol. However, those 9 patients were also included in the analysis, and each group therefore comprised 22 patients. The groups were designated 'm' (patients receiving the active substance) and 'p' (patients receiving the placebo). The general characteristics of the patients are shown in Table 1. At the study outset, there were no significant differences between the groups in terms of clinical variables (for asthma and for GERD), quality of life scores, or pulmonary function.

Among the patients with chronic respiratory symptoms and predominance of moderate/severe disease, as determined by the quantity of long-acting β_2-agonists and oral corticoids needed to control their symptoms, females predominated. Similarly, female patients with GERD presented high levels of esophageal acid exposure, especially in the evening, and the female patients presenting the greatest alterations were in the placebo group. Of the 44 patients studied, 9 (20%) presented asymptomatic GERD. Regarding the control of GERD in both groups, there was pronounced improvement in the 'm' group in terms of the symptoms score as well as in terms of the pH-metry readings. Only one patient in this group continued to present an abnormal DeMeester score at the end of the three-month follow-up period. There was an improvement in the symptoms score in both groups. However, this improvement was statistically significant only in the 'm' group. Nevertheless, the differences between the groups were not significant when evaluated at the study endpoint. Regarding quality of life, the 'm' group presented significant improvement in some of the quality of life score domains. However, when the groups were compared at the study endpoint, statistically significant differences were found only in the overall score. Nevertheless, a tendency toward improvement in all domains was found for the 'm' group (Table 2). Pulmonary function test results for both groups are shown in Table 3.

Regarding the presence of reflux-associated respiratory symptoms (RARS), the patients were

Table 2 - Comparison between the study outset and study endpoint, as well as between the two groups at the study endpoint, in terms of the clinical control of asthma variables and quality of life.

Variable	Placebo			Medication			p between groups
	Initial	Final	p	Initial	Final	p	
Diurnal SS*	68.8 ± 26	64.92 ± 4	0.29	69.2 ± 29	58.9 ± 23	0.01	0.11
Nocturnal SS	66 ± 25	63.42 ± 6	0.24	66.92 ± 7	57.9 ± 23	0.01	0.16
Total QoL*	63.8 ± 13	61.8 ± 13	0.25	61.61 ± 5	48.7 ± 12	0.00	0.001
Physical lim. QoL	60 ± 20	58.1 ± 18	0.31	63.7 ± 15	52.81 ± 7	0.02	0.67
Symptoms QoL	47.3 ± 23	53.4 ± 24	0.18	55.42 ± 6	40.8 ± 15	0.05	0.08
Compliance QoL	47.8 ± 26	42.22 ± 6	0.46	53.62 ± 4	37.42 ± 7	0.08	0.55
Socioecon. QoL	61.31 ± 9	59.72 ± 1	0.62	60.4 ± 20	56.31 ± 9	0.39	0.58
Psychosocial QoL	56 ± 13	51.61 ± 7	0.33	58 ± 22	43.62 ± 3	0.03	0.11

SS: symptoms score; QoL: quality of life, points; lim.: limitation; Socioecon.: Socioeconomic; and *mean ± standard deviation.

divided into two groups: 'RARS-positive' and 'RARS-negative'. Of the 44 patients evaluated, 7 were excluded from these groups due to the fact that there were insufficient data for this analysis. Table 4 shows the initial characteristics of these two groups; there were no significant differences. Subsequently, in order to test whether the presence of RARS is a predictive factor for the improvement of respiratory parameters, only the RARS-positive group was investigated, by means of comparisons prior to and after the therapeutic intervention, as well as by comparing the RARS-positive members of the 'm' group with those of the 'p' group. There was no improvement in the respiratory function values in either group, whether studied in isolation or compared at the study endpoint (Table 5).

Discussion

In the present randomized placebo-controlled study, we evaluated the treatment of GERD in patients with asthma over a three-month period. The correlation between these two diseases has been widely studied in the literature by means of clinical trials in which the role that the treatment of GERD plays in reducing asthma symptoms has been evaluated.[16,19-21] Despite the results, the issue remains controversial. In recent years, two large reviews were published, both addressing the impact that the treatment of GERD has on asthma control. In the first review,[11] it was concluded that the treatment of GERD reduced asthma symptoms in 69% of the cases, cut the use of asthma medication in 62%, and improved afternoon PEF in 26%. In the second review,[13] it was concluded that treatment of GERD did not consistently improve asthma symptoms. In addition, it neither reduced the use of medication nor had a significant effect on pulmonary function. However, the authors admitted that the studies included in these reviews presented methodological limitations, highlighting the need for other clinical trials involving this question. One of the controversial points reported by these authors was that, among the clinical trials reviewed, only six made

Table 3 - Comparison between the study outset and study endpoint, as well as between the two groups at the study endpoint, in terms of the respiratory variables.

Variable	Placebo			Medication			p between groups
	initial	final	p	initial	final	p	
FVC (% predicted)*	85.81 ± 5	85.9 ± 16	0.57	79.5 ± 17	81.3 ± 18	0.79	0.40
FEV_1 (% predicted)*	60.4 ± 19	58.9 ± 13	0.55	61.6 ± 19	62 ± 21	0.46	0.65
FEV_1/FVC (% predicted)	69.4 ± 13	70.2 ± 12	0.16	71.7 ± 11	73.8 ± 14	0.54	0.40
Diurnal PEF (L/min)*	264 ± 86	267 ± 81	0.59	317 ± 126	327 ± 77	0.23	0.74
Nocturnal PEF (L/min)	261 ± 83	269 ± 77	0.39	307 ± 121	323 ± 127	0.46	0.10

PEF: peak expiratory flow; FVC: forced vital capacity; FEV_1: forced expiratory volume in one second; and *mean ± standard deviation.

Table 4 - Comparison between the groups with and without reflux-associated respiratory symptoms at the study outset.

Variable	Positive RARS (n = 15)	Negative RARS (n = 22)	p
Nocturnal asthma SS*	78 ± 22	58 ± 25	0.15
Diurnal asthma SS	80 ± 22	59 ± 26	0.17
FEV_1 (% predicted)*	66 ± 24	59 ± 14	0.31
FEV_1/FVC (% predicted)	75 ± 11	70 ± 11	0.19
FVC (% predicted)*	87 ± 11	80 ± 12	0.24
GERD SS	15 ± 6	11 ± 9	0.12
PEF (diurnal)	314 ± 90	286 ± 120	0.43
PEF (nocturnal)	308 ± 81	287 ± 111	0.52
DeMeester score	30 ± 11	35 ± 22	0.36
% time standing	8.1 ± 3	7.4 ± 7	0.67
% time supine	6 ± 6	10 ± 8	0.12
% total time	7.4 ± 2.5	9 ± 6	0.33
Overall QoL	61 ± 15	66 ± 14	0.30

RARS: reflux-associated respiratory symptoms; SS: symptoms score; PEF: peak expiratory flow; FVC: forced vital capacity; FEV_1: forced expiratory volume in one second; QoL: quality of life score (points); and *mean ± standard deviation.

use of proton pump inhibitors. In addition, these studies showed that patients with respiratory manifestations of GERD require higher doses of proton pump inhibitors for the control of symptoms.[22] Based on these data, we chose to perform another 24-h pH-metry at the study endpoint in order to determine the true efficacy of the acid suppression instituted, with the objective of facilitating the analysis of the results.

In the present study, there was considerable esophageal acid suppression in the 'm' group patients, only 1 of which presented an abnormal DeMeester[15] score at the study endpoint. These findings might be explained by the use of a proton pump inhibitor, administered in appropriate doses over the course of the study. Other authors made use of this resource with the same objectives and concluded that acid ablation at the study endpoint was an important factor in the context of treatment and verification of its results.[22,23]

The population evaluated in our study included patients with asthma making continuous use of corticosteroids, and most of these patients also needed concomitant use of long-acting β_2-agonists

Table 5 - Comparison between the study outset and study endpoint, as well as between the two groups at the study endpoint, in terms of the variables studied and limited to the RARS-positive patients.

Variables	Positive RARS (n = 15)						
	Placebo (n = 8)			Medication (n = 7)			p between groups
	Initial	Final	p	Initial	Final	p	
Diurnal asthma SS*	90 ± 16	92 ± 17	0.30	80 ± 21	60 ± 24	0.05	0.02
Nocturnal asthma SS	81 ± 15	80 ± 14	0.39	77 ± 25	59 ± 27	0.04	0.03
Diurnal PEF (L/min)*	284 ± 98	300 ± 92	0.66	323 ± 86	334 ± 82	0.47	0.62
Nocturnal PEF (L/min)	266 ± 94	311 ± 90	0.35	324 ± 67	320 ± 72	0.68	0.84
FVC (%)*	91 ± 16	94 ± 16	0.60	81 ± 11	85 ± 19	0.22	0.49
FEV_1 (%)*	64 ± 23	64 ± 27	0.29	68 ± 17	73 ± 20	0.11	0.53
Overall QoL *	60 ± 19	62 ± 16	0.33	62 ± 8	46 ± 8	0.01	0.01

RARS: reflux-associated respiratory symptoms; SS: symptoms score; PEF: peak expiratory flow; FVC: forced vital capacity; FEV_1: forced expiratory volume in one second; QoL: quality of life score (points); and *mean ± standard deviation.

for their treatment. Despite this treatment, many patients presented diurnal and nocturnal symptoms, as well as quality of life limitations, suggesting that this population of patients presented more severe asthma. In very few studies in the literature, comparing the use of proton pump inhibitors with placebo, it has been described or suggested the severity of the respiratory disease. One of the therapeutic trials, in which the clinical severity of the patients studied was mentioned, was an open study.[22] This factor is important because the lack of information regarding the degree of severity in the beginning of the protocol might be another bias factor in these studies, since patients with more severe diseases are less likely to present pronounced improvement.

In the present study, esophageal manometry showed that, for both groups, the tonus of lower esophageal sphincter was at the lower limit of normality at the study outset. This finding coincides with the findings of another study previously conducted in our esophageal function laboratory,[24] in which the mean lower esophageal sphincter tonus was also at the lower limit of normality (15.3 mmHg). In that same study, the analysis of the esophageal motor profile of 164 patients with asthma submitted to esophageal manometry showed the presence of motor alterations in 32% of the individuals, most of which were represented by hypomotility or ineffective motility of the distal esophagus. In a similar study,[25] the incidence of manometry alterations was also reported to be higher in patients with asthma than in control group patients, and the most common disturbance (observed in 53%) was ineffective esophageal motility. In both studies, the authors suggested that the combination of abnormal pH-metry values and esophageal dysmotility might indicate microaspiration of gastric acid as a triggering, aggravating, or maintenance factor for respiratory symptoms in this population.

In concordance with other studies described in the literature,[26,27] our analysis revealed no changes in the respiratory function of the patients treated with acid ablation. This paradox was also found in other studies in which the clinical, or even surgical, treatment of GERD improved asthma symptoms, although there was no improvement in the pulmonary function of these patients. The limitations already described in this study and others, such as the small number of patients, or even the extremely short time of acid ablation, might have contributed to these results. These findings might also be explained by evidence showing an increase in minute ventilation as a triggering factor of dyspnea and thoracic discomfort in patients submitted to esophageal acid perfusion, although there was no airway obstruction.[28]

Field *et al.*[28] investigated, by means of a GERD/asthma questionnaire, the presence of RARS. Harding *et al.*[16] later identified this condition as a predictive factor for treatment response. It is currently believed that this group of patients, consisting of those diagnosed with asthma and concomitant GERD who report respiratory symptoms directly related to reflux, responds better to anti-reflux measures and drug treatment, consequently presenting better asthma control when being treated for GERD. In our study, we also evaluated the presence of RARS by means of a questionnaire, and most subjects did not present RARS. Some initial characteristics of the patients were also compared by stratifying them on the basis of the presence/absence of RARS in order to better define this group of patients with asthma, and no significant differences were found. Nevertheless, when only the patients with RARS were studied in terms of the study outcome measures, we again found a significant difference in the improvement of the symptoms and the quality of life scores in the 'm' group. Therefore, we can infer that the study of this characteristic in patients with asthma and symptomatic GERD might be important for informing decisions regarding the treatment of such patients.

Since this was a randomized prospective double-blind study with a complex methodology, some deficiencies and limitations must be mentioned. The final sample was small, which might have contributed for the lack of more significant findings related to the outcome measures studied. In clinical trials involving larger patient samples, such as that of Kiljander *et al.*,[19] which involved 57 patients in a controlled crossover study, there was a 20% functional improvement in 35% of the patients treated. In addition, the three-month follow-up period employed in the present study might have been too short for the identification of consistent improvement in the respiratory function parameters of the patients evaluated.

As knowledge of the extra-esophageal manifestations of GERD increases, so does the need for

a thorough study on the prevalence of GERD in a non-referenced (*i.e.* bias-free) population of subjects with asthma. Such a study should also include the objective confirmation of abnormal esophageal exposure to gastric acid. In addition, there is sufficient evidence to show that there is much to be done regarding therapeutic intervention in this population of patients. It is imperative to determine what characteristics of these patients with asthma could be used as predictors of the response to GERD therapy, as well as what parameters would be the most appropriate for the assessment of GERD. We therefore conclude that, in the present study, GERD treatment significantly improved the quality of life and the symptoms scores of the patients with asthma. However, there were no significant alterations in their respiratory function parameters. Among the patients studied, those who presented RARS and were submitted to pharmacological acid ablation were the ones who also presented objective reductions in their asthma score, as well as an improvement in their quality of life at the end of the evaluation period.

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