e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2023; 15(9); 1096-1101

Original Research Article

The Impact of Treating Allergic Rhinitis with a Combination of Medications on Bronchial Asthma and Vice Versa

Pramod Prabhakar

Assistant Professor, Department of (ENT), Lord Buddha Koshi MedicalCollege and Hospital, Saharsa, Bihar, India

Received: 25-06-2023 / Revised: 28-07-2023 / Accepted: 30-08-2023
Corresponding author: Dr. Pramod Prabhakar
Conflict of interest: Nil

Abstract:

Introduction: Asthma and allergic rhinitis are regarded as two distinct manifestations of the same allergic disease. It is still unclear if treating rhinitis-related inflammation leads to improvements in asthma or vice versa. To examine how bronchial asthma and allergic rhinitis are affected by a combination of drugs was the main objective.

Method: Patients who displayed both allergic rhinitis and bronchial asthma symptoms were chosen and split into two groups of 60 each. Patients in group 1 had nasal symptoms before pulmonary symptoms. Patients in group 2 were those whose lung symptoms appeared before their nasal symptoms. Following an 11-week treatment period, the effectiveness of intranasal fluticasone and fexofenadine in treating asthma symptoms was evaluated using the pulmonary function test (PFT) and asthma control test (ACT). After 11 weeks, the effectiveness of the combination of inhaled budesonide and salbutamol/formeterol on the symptoms of allergic rhinitiswas evaluated in all group 2 patients using the Total Nasal Symptom Score (TNSS) and Visual Analogue Score (VAS).

Observation: Patients ranged in age from 24.4±1.53 years on average, with 90 men and 30 women. After 11 weeks, group 1 patients' mean FEV1/FVC climbed from 63.43 to 68.055 and their average ACT score went from 16.66 to 19.77 (both p values <0.04). The mean VAS score for all symptoms decreased post-treatment in group 2 and the mean TNSS value decreased from 8.817 to 2.8 (both p values 0.04).

Conclusion: Thus, the therapeutic relationships between the two disorders that we discovered in this study pointed to the necessity for a coordinated strategy to the care of both diseases.

Keywords: Intranasal Corticosteroids, Allergic Rhinitis, Bronchial Asthma, Combined AirwayDisease.

Introduction

Asthma and allergic rhinitis frequently coexist as comorbid conditions. In recent years, there has been a lot of attention in the relationship between upper and lower airway illnesses. It is known that nasal allergy and asthma regularly co-occur, with up to 80% of asthmatics also experiencing persistent nasal symptoms and 20–50% of allergic rhinitis patients also having co-occurring asthma. But it's still unclear if lung disease comes before nasal disease or the other way around.

The therapeutic link between the two disorders has been the subject of numerous investigations in the past. When applied to the bronchi and nose, topical glucocorticosteroids are the most effective medications for treating rhinitis and asthma, respectively. Most studies demonstrated that administering glucocorticoids intranasally to treat allergic rhinitis improved asthma symptoms. Orally administered medications may have an impact on bronchial and nasal symptoms. Although some studies have found a minor effect on asthma symptoms, oral H1-antihistamines are not advised for the treatment of asthma [1]. They are the first-line treatment for allergic rhinitis.

It was discovered that oral H1-antihistamines and decongestants worked better together to treat asthma symptoms [2]. However, very few studies have examined the impact of treating asthma with a medication combination for allergic rhinitis and vice versa. Additionally, there are relatively few research on the impact of treating asthma with inhaled glucocorticoids and SABA/LABA on nasal illness.

Method

This prospective study ran from October 2020 to March 2021 in a tertiary care facility. After obtaining the necessary written agreement, a total of 120 patients with symptoms of bronchial asthma and allergic rhinitis that were indoor patients and

attending the outpatient department were included in the study. Recent ARIA criteria were used to make the diagnosis of allergic rhinitis, and recent GINA standards were used to make the diagnosis of bronchial asthma. The patients who were chosen for the trial were assessed with an accurate history and thorough physical. The Lord Buddha Koshi Medical College and Hospital ethical committee granted the necessary ethical clearance.

Age >10 years; patients exhibiting both pulmonary (asthma) and nasal (allergic rhinitis) symptoms. Patients with solely bronchial asthma or allergic rhinitis symptoms are excluded. Affected by systemic conditions like hypertension, uncontrolled diabetes, and heart disease. They were split into two groups based on the previous symptom history.

Group 1: Patients in this group had allergic rhinitis, which manifested as nasal symptoms before bronchial asthma symptoms.

Patients in group 2 were those whose pulmonary symptoms (bronchial asthma) appeared before their nasal symptoms (allergic rhinitis).

According to ARIA recommendations, all patients in group 1 received treatment with fluticasone propionate, an intranasal corticosteroid, and fexofenadine, an oral antihistamine. The effectiveness of the treatment of asthma symptoms was evaluated using spirometry (Pulmonary Function Test) and the Asthma Control Test (ACT).

According to GINA recommendations, all of the patients in group 2 received inhaled corticosteroids (budesonide) and short- and long-acting beta agonists (salbutamol/formoterol) to treat their allergic rhinitis symptoms. The effectiveness of their treatment was measured using the Total Nasal Symptom Score (TNSS) and Visual Analogue Score (VAS).

Control test for asthma (ACT)

The amount of asthma control is determined by the asthma control test, a particular form of a questionnaire-description score. The patient uses a self-administered instrument. It has five questions and a three-week memory period (on symptoms and daily functioning). Symptoms and activities are rated on a 5-point scale (1 = always to 5 = never; asthma control rating: 1 = not at all controlled to 5 = entirely controlled). Higher scores indicate better asthma control. The scores range from 5 (poor control of asthma) to 25 (full control of asthma). An ACT score of 19 or higher denotes asthma under control. ACT evaluates the frequency of wheezing and other general asthma symptoms, the use of rescue drugs, and how asthma affects everyday life.

Nasal Symptom Score Overall (TNSS)

This sort of score is subjective. By assessing the severity of the patient's symptoms during the past 10 hours, daily patient diaries were used to record TNSS. As the result of adding together the four nasal symptoms of rhinorrhea, nasal itching, nasal congestion, and sneezing, each of which was graded on a scale from 0 (no signs/symptoms obvious) to 3 (signs/symptoms producing severe discomfort that interfered with everyday activities), The change from baseline in the mean patient-reported TNSS value averaged during the treatment period of two months (14 days) and 14 days was the primary outcome.

Defined symptoms scores Score Grade Instructions 0- None No observable symptom or indicator

1. Mild Symptom/Sign definitely present, but little awareness; tolerable.
2. Moderately clear awareness of signs or symptoms that may be uncomfortable but are tolerable 3- A severe symptom or sign that is difficult to bear interferes with the challenge session's activities Score in visual analogue (VAS)

A Visual Analogue Score (VAS) is a 10 cm long measurement tool that aims to measure a characteristic or attitude that is thought to fall along a value continuum and is difficult to measure directly. The VAS scale has scores ranging from 0 (no symptoms) to 10. (Very severe symptoms). The VAS score might develop into a very straightforward and accurate assessment that might serve as both a key clinical practise indicator and a major endpoint in clinical studies. According to the results of the characteristic curve, individuals with a VAS of less than 4 cm were likely to have mild rhinitis (negative predictive value: 93.4%), whereas those with a VAS of more than 5 cm were likely to have moderate or severe rhinitis (positive predictive value: 73.5%). Significant correlations between visual analogue scales were found ($P< 0.0002$).

Results

The total number of males was 72, whereas there were only 48 females. 37 males and 23 females made up Group 1. Table 1 show that there were 35 men and 25 women in Group 2.

Table 1: Group-wise gender distribution

Gender	Group 1		Group 2	
	No. of Patients	Percentage	No. of Patients	Percentage
Male	37	56%	35	62%
Female	23	44%	25	38%
Total	60	100%	60	100%

Age-based breakdown: The mean age of the study's patients was 24.4 + 1.53 years, with the youngest patient being 11 years old and the oldest being 61 years old. According to Table 2, the majority of patients in Group 1 (41%) and Group 2 (37%) were between the ages of 10 and 21.

Table 2: Age distribution of patients in groups 1 and 2

Age	Group 1		Group 2	
	No. of Patients	Percentage	No. of Patients	Percentage
10-20	15	30%	25	36%
21-30	30	40%	19	26%
31-40	10	15%	7	16%
41-50	3	20%	6	12%
>51	2	5%	3	10%
Total	60	100%	60	100%

When the chi-square test was used on the aforementioned data, it was discovered that there was no significant difference between the groups in terms of the distribution of patients' ages and genders.

Effect of allergic rhinitis medication on bronchial asthma PFT - most patients' FEV1/FVC values improved throughout monthly follow-up for 11 weeks. On the other hand, symptoms of asthma in 2 patients grew worse. The mean FEV1/FVC increased from 63.43 before therapy to 68.055 after treatment.

The pre-treatment and post treatment mean scores were compared using the Kolmogorov-Smirnov (KS) test, and it was discovered that this comparison was statistically significant (p value < 0.04) (h=2, p=0.038 from the KS test).

All group 2 patients received the ACT questionnaire for asthma, and a maximum of 11 weeks of follow-up were conducted. The mean ACT score rose from 16.66 before therapy to 19.77 after 11 weeks. One patient, though, saw a score decline. The two-month pre-treatment and post treatment mean scores were compared using the Kolmogorov-Smirnov (KS) test, which was determined to be statistically significant. (h=2, p=0.00005 from the KS-test; p value 0.04)

Influence of bronchial asthma therapy on allergic rhinitis: All patients received the Total Nasal Symptom Score (TNSS) questionnaire, which was used to compare their pre- and post-treatment symptoms. The average TNSS value dropped from 8.817 to 2.938.

Discussion

Recently, Lohia R et al meta-analysis [9] found 23 studies evaluating the effectiveness of intranasal corticosteroids in treating patients with allergic rhinitis and asthma. A high proportion of patients in otorhinolaryngology OPDs are caused by allergic rhinitis and bronchial asthma, which are two of the 23 studies with sufficient data. The link between the two diseases in terms of clinical, pathophysiological, and therapeutic features has been the subject of numerous investigations. In the same patient, allergic rhinitis and bronchial asthma are common. BP and Yunginger JW et al [3] discovered that 20–40% of patients with allergic rhinitis had bronchial asthma. About 80% of people with bronchial asthma also reported nasal symptoms, according to Coren J et al [4]. In a different study [5] on children, Sawako Masuda et al. discovered that 83.8% of the asthmatic children had persistent nose symptoms. Numerous anatomical, physiological, and pathological bases can be used to explain the high concordance of the two disorders. One morpho- functional unit that can be thought of as a whole is respiratory system. It is completely covered by ciliated epithelium, mucinous glands, a large vasculature, and innervation (similar in the upper and lower airways [6]), up until the smaller bronchi.

Response of One Disease's Therapy to Another In our investigation, we discovered that one disease's treatment had a considerable effect on another disease. Intranasal corticosteroids and antihistamines were administered to patients with allergic rhinitis who also had bronchial asthma, and the effectiveness of the treatment was assessed using the PFT and Asthma Control Test. Patients with bronchial asthma who also had allergic rhinitis were treated with inhaled corticosteroids, SABA/LABA, and it was determined how well they were responding to the symptoms of allergic rhinitis by using TNSS and VAS. Using the 4% significance level of the two- sample Kolmogorov-Smirnov (KS) test with the MATLAB Toolbox, we

examined the change in indices over time. At 5 weeks and 11 weeks, the pre-treatment score and the post treatment mean scores were observed.

Patients in group 1 experienced a significant increase in their mean FEV1/FVC and asthma control test scores over an 11-week period from their pre-treatment to post treatment values. For a period of 11 weeks, participants in group 2's mean TNSS and mean VAS scores (for all four symptoms) significantly decreased from pre-treatment to post treatment scores. To evaluate how one disease responds to treatment when applied to another, numerous other researches with comparable findings have been conducted in the past.

In their study, Rafael Stelmach et al. [7] examined nasal and pulmonary symptoms, pulmonary function, and bronchial hyperreactivity in patients receiving inhaled corticosteroids to those getting a placebo after 4 weeks and 16 weeks of treatment. When given corticosteroids, patients showed a gradual and significant improvement in their nasal and pulmonary symptoms, which began after 4 weeks (p 0.05) and persisted through the completion of the course of treatment (p 0.001). The three groups showed a reduction in asthma-related morbidity (p 0.05), which was measured by quantifying absence from regular employment, hospital emergency visits, and night awakenings. Intranasal topical corticosteroids significantly decreased the global rhinitis symptom scores in all patients, according to Wade T. A. et study [8].'s (p = 0.05). The patients' baseline symptom ratings for rhinitis were 3.1±0.3. After receiving intranasal beclomethasone, rhinitis symptom ratings fell to 1.72 ±0.2.

In a recent meta-analysis, Lohia R et al [9] found 23 trials that evaluated the effectiveness of intranasal corticosteroids in treating allergic rhinitis and asthma in patients. Of the 23 trials, 18 studies—including 14 parallel and four cross-over randomised, placebo-controlled trials—had sufficient data to allow for analysis. A total of 2162 individuals were involved in the studies, 1659 of them finished the entire trial, while 503 patients did not follow up. The biggest number of participants came from three of the 18 studies: 509 patients from Nathan et al., 366 patients from Katial et al., and 236 patients from Dahl et al. Patients enrolled in the remaining trials ranged in size from 16 to 90.

They came to the conclusion that in people with both AR and asthma, intranasal corticosteroid medicines dramatically improved some outcome indicators related to asthma. When patients were not taking daily orally inhaled corticosteroids or when the corticosteroid drugs were inhaled into the lungs through the nose, this impact was most pronounced with intranasal corticosteroid sprays. The role of nasal inhalation therapy as a monotherapy in individuals with both asthma and AR, as well as the role of intranasal corticosteroid sprays as asthma therapy, both require further study. Approximately 73% of the 4944 individuals with allergic asthma symptoms evaluated by Crystal- Peters et al. [10] were also being treated for allergic rhinitis. When comparison to the treated group, the untreated group experienced asthma-related symptoms more frequently (6.6% vs. 1.3%). Asthma-associated events were about half as likely to occur in the treated group as in the untreated group, according to an incidence related density ratio of 0.49 for the treatment group (P =.001).

For people who have both rhinitis and asthma, they may indirectly improve asthma symptoms. Cetirizine 10 mg was able to considerably lessen asthma symptoms during the pollen season in a placebo-controlled research involving 186 individuals with seasonal allergic rhinitis and asthma [11]. Another trial found that giving individuals with seasonal allergic rhinitis and mild asthma a combination of loratadine 5 mg and pseudoephedrine 120 mg twice day could dramatically improve asthma-related events, peak expiratory flow, and lower albuterol intake [2]. In combination with inhaled corticosteroids, like in our trial, fexofenadine may have an additional impact, according to one small study [12]. Overall, the positive effects of this class of medications are modest, but they may be particularly significant in patients who also use inhaled corticosteroids and have mild intermittent asthma and concurrent nasal allergies.

Although not significantly, we also noticed a decrease in symptoms including runny nose, sneezing, and rhinorrhea when inhaled glucocorticosteroids and SABA/LABA were used. Similar outcomes were observed by Greiff et al [13] using inhaled budesonide. This finding confirms the theory put forth by Bucca et al. [14] that attacks of asthma and rhinitis are both brought on by extra thoracic receptors triggered by inflammatory processes in the upper airways. Patients with rhinitis asthma who also have BHR and extra thoracic hyper reactivity may have an allergy based impairment affecting all airways, as evidenced by the improvement in both nasal and pulmonary symptoms following treatment. [15]

Uncertainty surrounds the beta agonist's function in nasal allergies. High intranasal dosages of SABA fenoterol have been demonstrated to quickly reduce allergen-induced nasal obstruction, sneezing, and rhinorrhea in studies using allergen challenges, which most likely results from the dilatation of capacitance vessels [16]. Additionally, this medication has been shown to affect basophils and mast cells' production of mediators [17,18]. Prior to each of the several challenge doses of the allergen,

high-dosage topical terbutaline (1 mg) was administered repeatedly and led to significant suppression of symptoms generated solely by the highest allergen dose [19]. Another trial has demonstrated the effectiveness of oral salbutamol in treating seasonal allergic rhinitis brought on by pollen, lowering symptoms, the need for antihistamines, and the rise in blood IgE levels [20]. Despite the intriguing results produced with SABAs, the available LABA trials are largely unfavourable. Salmeterol intranasal dosage (50 g for 4 weeks) was administered to 12 asymptomatic people with a history of seasonal allergic rhinitis in a randomised double-blind placebo-controlled crossover experiment, however it was unsuccessful in reducing sneeze and the overall symptom score[21]. Other studies utilising formeterol have also shown that LABAs are ineffective in treating allergic rhinitis [22]. Regardless of the initial target organ, Denburg et al research [23].'S showed that the allergic response has a generalised systemic effect. The significant accumulation of eosinophils in asthmatic patients' airways appears to be the result of a final, systemic reaction to the on-going recruitment of basophils, eosinophils, and progenitor cells from the bone marrow.

A bidirectional link between nasal and bronchial inflammation was shown by Braunstahl et al. [23]. The amount of eosinophils in the nasal and bronchial mucosa increased 24 hours following allergen bronchoprovocation, according to a preliminary investigation. In a subsequent study [24], nasal provocation led to an increase in eosinophils in the nasal and bronchial epithelium, which was positively correlated with increases in vascular cell adhesion molecule, intracellular adhesion molecule, and E-selectins in vessels supplying the nasal and bronchial tissue primarily. We can speculate that intranasal corticosteroids may act in the lungs and inhaled corticosteroids may act in the nasal mucosa given this bidirectional pathophysiology.

Our observation that some patients' asthma and rhinitis might be completely managed by intranasal topical treatment is consistent with the fact that corticosteroids, despite being applied locally, have such a systemic effect. Less than 2% of the nasal drug was transported to the lungs, making it extremely improbable that the intranasal corticosteroid had a direct anti-inflammatory effect on the lungs. The overall amount of corticosteroids consumed and absorbed by the digestive system would not be sufficient to account for the anti-inflammatory effect. A direct topical action in the lungs rather than systemic absorption was the cause of the therapy's anti-inflammatory effect, according to earlier investigations of asthma treatment with inhaled corticosteroids [25].

These findings might potentially be explained by the likely neuromechanisms. In awake and anaesthetized dogs, stimulation of the nasal mucosa resulted in a "nasopulmonary response" and a subsequent rise in pulmonary airway resistance. A similar reaction in humans may be inhibited by topical corticosteroids [26].

Conclusion

Therefore, based on the results of our study, we can conclude that failing to treat concomitant rhinitis may compromise clinical control of asthma. Although there were significantly fewer participants in this trial, they were closely monitored for over 12 weeks. The patient may need higher doses of oral corticosteroids and may exhibit increased morbidity if asthma is thought to be a pulmonary illness only. The sole use of medications for allergic rhinitis, on the other hand, can be used to control mild to moderate asthma. Overall, we can say that treating allergic rhinitis should be viewed as an essential component of treating asthma and vice versa.

References

1. Van Ganse E, Kaufman L, Derde MP, Yernault JC, Delaunois L, Vincken W. Effects of antihistamines in adult asthma: a meta-analysis of clinical trials. European Respiratory Journal. 1997 Oct 1; 10(10):2216-24.
2. Corren J, Harris AG, Aaronson D, Beaucher W, Berkowitz R, Bronsky E, Chen R, Chervinsky P, Cohen R, Fourre J, Grossman J. Efficacy and safety of loratadine plus pseudoephedrine in patients with seasonal allergic rhinitis and mild asthma. Journal of allergy and clinical immunology. 1997 Dec 1; 100(6):781-8.
3. Noone SA, Sicherer SH. Patient compliance with self-administered epinephrine (SAE) for food allergic (FA) children. J Allergy Clin Immunol. 1999 Jan 1; 103(1):S54.
4. Corren J. The impact of allergic rhinitis on bronchial asthma. Journal of allergy and clinical immunology. 1998 Feb 1; 101(2):S352-6.
5. Masuda S, Fujisawa T, Katsumata H, Atsuta J, Iguchi K. High prevalence and young onset of allergic rhinitis in children with bronchial asthma. Pediatric allergy and immunology. 2008 Sep; 19(6):517-22.
6. Undem BJ, McAlexander M, Hunter DD. Neurobiology of the upper and lower airways. Allergy. 1999 Nov; 54:81-93.
7. Stelmach R, Maria do Patrociínio TN, Ribeiro M, Cukier A. Effect of treating allergic rhinitis with corticosteroids in patients with mild-to-moderate persistent asthma. Chest. 2005 Nov 1; 128(5):3140-7.

8. Watson WT, Becker AB, Simons FE. Treatment of allergic rhinitis with intranasal corticosteroids in patients with mild asthma: effect on lower airway responsiveness. Journal of allergy and Clinical Immunology. 1993 Jan 1; 91(1):97-101.
9. Lohia S, Schlosser RJ, Soler ZM. Impact of intranasal corticosteroids on asthma outcomes in allergic rhinitis: a meta-analysis. Allergy. 2013 May; 68(5):569-79.
10. Crystal-Peters J, Neslusan C, Crown WH, Torres A. Treating allergic rhinitis in patients with comorbid asthma: the risk of asthma-related hospitalizations and emergency department visits. Journal of Allergy and Clinical Immunology. 2002 Jan 1; 109(1):57-62.
11. Grant JA, Nicodemus CF, Findlay SR, Glovsky MM, Grossman J, Kaiser H, Meltzer EO, Mitchell DQ, Pearlman D, Selner J, Settipane G. Cetirizine in patients with seasonal rhinitis and concomitant asthma: prospective, randomized, placebo-controlled trial. Journal of allergy and clinical immunology. 1995 May 1; 95(5):923-32.
12. Lee DK, Jackson CM, Haggart K, Lipworth BJ. Repeated dosing effects of mediator antagonists in inhaled corticosteroid-treated atopic asthmatic patients. Chest. 2004 Apr 1; 125(4):1372-7.
13. Greiff L, Andersson M, Svensson C, Linden M, Wollmer P, Brattsand R, Persson CG. Effects of orally inhaled budesonide in seasonal allergic rhinitis. European Respiratory Journal. 1998 Jun 1; 11(6):1268-73.
14. Bucca C, Rolla G, Brussino L, De Rose V, Bugiani M. Are asthma-like symptoms due to bronchial or extrathoracic airway dysfunction? The Lancet. 1995 Sep 23; 346(8978):791-5.
15. Bucca C, Rolla G, Scappaticci E, Chiampo F, Bugiani M, Magnano M, D'Alberto M. Extrathoracic and intrathoracic airway responsiveness in sinusitis. Journal of Allergy and Clinical Immunology. 1995 Jan 1; 95(1):52-9.
16. Grönneberg R, Raud J. Effects of local treatment with salmeterol and terbutaline on anti-IgE- induced wheal, flare, and late induration in human skin. Allergy. 1996 Oct; 51(10):685-92.
17. Borum P, Mygind N. Inhibition of the immediate allergic reaction in the nose by the beta-2 adrenostimulant fenoterol. Journal of Allergy and Clinical Immunology. 1980 Jul 1; 66(1):25-32.
18. Borum P, Mygind N, Larsen FS. The anti-allergic effect of the beta 2-adrenergic agent fenoterol in the nose. European Journal of Respiratory diseases. Supplement. 1983 Jan 1; 128:44- 9.
19. Svensson C, Greiff L, Andersson M, Alkner U, Grönneberg R, Persson CG. Antiallergic actions of high topical doses of terbutaline in human nasal airways. Allergy. 1995 Nov; 50(11):884- 90.
20. Proud D, Reynolds CJ, Lichtenstein LM, Kagey-Sobotka A, Togias A. Intranasal salmeterol inhibits allergen-induced vascular permeability but not mast cell activation or cellular infiltration. Clinical and Experimental Allergy: Journal of the British Society for Allergy and Clinical Immunology. 1998 Jul 1; 28(7):868-75.
21. Holt S, Suder A, Dronfield L, Holt C, Beasley R. Intranasal β-agonist in allergic rhinitis. Allergy. 2000 Dec; 55(12):1198-.
22. Denburg JA, Sehmi R, Saito H, Pil-Seob J, Inman MD, O'Byrne PM. Systemic aspects of allergic disease: bone marrow responses. Journal of allergy and clinical immunology. 2000 Nov 1; 106(5):S242-6.
23. Braunstahl GJ, Overbeek SE, Fokkens WJ, KleinJan A, McEuen AR, Walls AF, Hoogsteden HC, PRINS JB. Segmental bronchoprovocation in allergic rhinitis patients affects mast cell and basophil numbers in nasal and bronchial mucosa. American journal of respiratory and critical care medicine. 2001 Sep 1; 164(5):858-65.
24. Braunstahl GJ, Overbeek SE, KleinJan A, Prins JB, Hoogsteden HC, Fokkens WJ. Nasal allergen provocation induces adhesion molecule expression and tissue eosinophilia in upper and lower airways. Journal of Allergy and Clinical Immunology. 2001 Mar 1; 107(3):469-76.
25. Toogood JH, Frankish CW, Jennings BH, Baskerville JC, Borga O, Lefcoe NM, Johansson SA. A study of the mechanism of the antiasthmatic action of inhaled budesonide. Journal of allergy and clinical immunology. 1990 May 1; 85(5):872-80.
26. Whicker JH, Kern EB. The nasopulmonary reflex in the awake animal. Annals of Otology, Rhinology & Laryngology. 1973 May; 82(3):355-8.