Budesonide Nasal Spray Alone or in Combination with Cetirizine in Severe Seasonal Allergic Rhinitis

CİDDİ MEVSİMSEL ALERJİK RİNİTTE BUDESONİD NAZAL SPREYİN TEK BAŞINA VEYA SETİRİZİN İLE KOMBİNE KULLANIMI

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Summary

Objective: Administration of antihistamines in addition to topical corticosteroids is not uncommon in routine practice for patients with severe symptoms of allergic rhinitis although there is a lack of enough data on the efficacy of such a combination therapy. The aim of this study was to investigate the efficacy of budesonide alone or in combination with cetirizine on symptoms of allergic rhinitis in patients with severe seasonal allergic rhinitis.

Material and Methods: This randomised, placebo controlled, double-blind prospective clinical trial was performed in 214 patients with severe seasonal allergic rhinitis. Seventy-three patients received only budesonide aqueous nasal spray (400µg/day) and placebo tablets whereas 70 patients received budesonide aqueous nasal spray (400µg/day) in combination to cetirizine tablets (10 mg/day) for 3 weeks. Seventy-one patients received placebo spray and tablets for the same period. Reduction of nasal and ophthalmic symptom scores were compared between groups.

Results: Both treatment regimens were found to be effective for reducing nasal and ophthalmic symptom scores compared to the placebo. The combination regimen was not more effective than budesonide alone for controlling any parameter studied.

Conclusion: Budesonide nasal spray can be used alone for sufficient nasal and ocular symptomatic control with low incidence of side effects for patients with severe symptoms of allergic rhinitis. In case of insufficient symptomatic control, combination of an agent other than cetirizine may be considered.

Key Words: Hay fever, Budesonide, Cetirizine, Drug therapy, Combination

T Klin J E N T 200, 2:148-154

Özet

Amaç: Ciddi mevsimsel alerjik rinitli hastalarda antihistaminiklerle topikal kortikosteroidler günlük kullanımda sıklıkla kombine edilmekteyse de, bu kombinasyonun etkinliği hakkında yeterli veri yoktur. Bu çalışmanın amacı, budesonidin ciddi mevsimsel alerjik rinit semptomları üzerindeki etkinliğinin tek başına veya setirizinle kombine edildiği durumda araştırmaktı.

Materyal ve Metod: Bu randomize, plasebo kontrollü, çift kör, prospektif klinik çalışma ciddi mevsimsel alerjik rinitli 214 hasta üzerinde yapıldı. Yetmiş üç hastaya budesonid aqua nazal sprey (400µg/gün) ve plasebo tablet verilirken, 70 hastaya budesonid aqua nazal spreye (400µg/gün) ek olarak, setirizin tablet (10 mg/gün) üç hafta süreyle uygulandı. Yetmiş bir hastaya aynı süreyle plasebo sprey ve tablet verildi. Gruplar arasında nazal ve oftalmik semptomlardaki azalma karşılaştırıldı.

Bulgular: Plaseboyla karşılaştırıldığında her iki tedavi şeklinin nazal ve oftalmik semptomları azaltmada etkin olduğu görüldü. Kombinasyon tedavisi, çalışılan hiçbir parametrede budesonidin tek başına kullanımından daha etkin değildi.

Sonuç: Ciddi mevsimsel alerjik rinit semptomları olan hastalarda yeterli nazal ve oküler semptom kontrolü sağlayan ve az yan etkiye neden olan budesonid nazal sprey, tek başına kullanılabilir. Semptom kontrolünün yetersiz olması durumunda, setirizinden farklı bir ajanla kombinasyon planlanabilir.

Anahtar Kelimeler: Alerjik rinit, Budesonid, Setirizin, İlaç tedavisi, Kombinasyon

T Klin K B B 2002, 2:148-154

Allergic rhinitis is the most common one, among chronic allergic respiratory tract disorders and it affects approximately 20-25% of the population (1). Itching and irritation of the nose, sneezing, nasal discharge and nasal obstruction are the main symptoms. Eye, ear and throat itching, edema around the eye, headache, sleeping disorders and difficulty of concentration may be the accompanying symptoms (2).

Allergic rhinitis may be perennial or seasonal according to the duration and timing of the symptoms. Airborne allergens and especially pollens are responsible for seasonal allergic rhinitis.

The aim of pharmacotherapy for seasonal allergic rhinitis is to achieve sufficient symptomatic control. This goal may be difficult especially in patients with severe symptoms although many options as antihistamines, decongestants, systemic and nasal corticosteroids and mast cell stabilizers are available for the management of the disease (3-6). Antihistamines and topical corticosteroids are the most widely used medications (7,8) and their concomitant use is not uncommon in the clinical practice. In fact there are only a few studies in the literature in which the clinical efficacy of such combinations have been investigated (9,10). None of these studies focuses on patients with severe seasonal allergic rhinitis.

In this study, we compared the efficacy of budesonide nasal spray alone and in combination with cetirizine tablets, on patients with severe seasonal allergic rhinitis.

Material and Methods

Patient selection

Patients who were admitted to the ENT or Chest Diseases Policlinic with the symptoms of allergic rhinitis during 3 consecutive pollen seasons (between March 1-June 30, 1999, 2000, 2001) were considered as candidates for the study. Patients with known seasonal allergies were not included in the study outside of the pollen season. A detailed history, complete otolaryngological examination and paranasal sinus X-rays (Waters and Caldwell views) were obtained from all of the patients. Patients with normal sinus X-rays were sent to the laboratory for total serum IgE counts and in vitro specific IgE testing for grasses and trees. In vitro testing for specific IgE was performed with the "coated microtiter enzyme immunoassay" method, using Dr.Fooke equipment. If the specific IgE results were also positive (>0.35 IU/ml) for the mentioned allergen(s), patients were included in the study. A prick test for the same allergens was applied to the patients with negative in vitro IgE results. Patients with positive prick tests for at least one of the allergens were also included in the study.

An informed consent was obtained from all patients or their parents. The study was approved by the local review board and was performed in accordance with the Declaration of Helsinki.

Symptom scores

Patients were questioned by one of the investigators for the symptoms of allergic rhinitis ie. sneezing, nasal discharge, nasal obstruction, postnasal drip, nose/throat itching, and eye irritation/watery eye. The symptoms were scored as follows: 0- no symptom, 1- mild symptom, 2- moderate symptom, and 3- severe symptom. The scores for individual symptoms were summed up to calculate *total pre-treatment symptom scores*.

The patients were assumed to have *mild* symptoms if their total pre-treatment symptom scores were between 0-5; *moderate* symptoms if their total scores were between 6-11; and *severe* symptoms if their total scores were equal to or greater than 12. Only the patients with total scores equal to or greater than 12 were included in the study.

Patients and study groups

This prospective, randomised, double-blind, placebo controlled clinical trial was performed on 214 patients with severe seasonal allergic rhinitis, who fulfilled the criteria mentioned above. Their ages ranged between 15-63 years. The patients were randomly divided into three groups.

The "Budesonide group" (BG) consisted of 73 patients and received Budesonide aqueous nasal spray (Rhinocort aqua® spray) 400µg/day in two divided doses and placebo tablets for 21 days. The "Combination group" (CG) consisted of 70 patients and received budesonide aqueous nasal spray 400µg/day in addition to cetirizine tablets (Zyrtec®) per oral 10 mg/day once a day. Seventy-one patients received placebo spray and tablets for the same period and were called as "Placebo group" (PG).

Physical examination and respiratory function tests were performed in all patients before and after

the therapy. The respiratory function tests were performed using "Minato Autospirometer". The patients were diagnosed to have mild asthma if FEV1/FVC was between 60-79%, moderate asthma if this rate was 40-59% and severe asthma if the rate was <40%.

Follow-up

Patients received therapy for 3 weeks and were called for follow-up. Post-treatment symptoms were questioned and scored as mentioned above by an investigator who was unaware of the type of the therapy. An otolaryngological examination was performed. The symptom scores were summed up to calculate total post-treatment symptom scores. The post-treatment symptom scores for eye symptoms were also recorded. Patients were asked to make a global assessment of the efficacy of treatment as *ineffective, slightly effective, moderately effective* or *very effective.*

Probable side effects of the medications mentioned on their prospectus were questioned, and if present, were recorded.

Statistical analysis

The Wilcoxon test was applied to identify the difference between pre-treatment and post-treatment symptom scores. The Mann Whitney-U test was applied to identify the difference between the post-treatment symptom scores and the overall assessment of the therapy for the two groups. If $p<0.05$, the result was accepted as statistically significant.

Results

The number of the patients with severe symptoms for each study parameter is presented in Figure 1. The most common severe symptoms were nasal discharge and nasal obstruction.

Efficacy

Overall assessment of the therapy: Figure 2 shows the results of the patients' overall assessment of the efficacy of the therapy. Thirty-five (47.9%) patients in the BG and 31 patients (44.3%) in the CG reported their therapy as *very effective*. Only 10 patients (14.1%) in the PG reported the therapy as *very effective*. The difference between the BG and the CG was not statistically significant ($p>0.05$). The differences between the BG-PG and CG-PG were significant ($p<0.05$). None of the patients in the BG and the CG reported the therapy as ineffective whereas this number was 18 in the PG.

Mean total symptom scores: Mean total symptom scores were 13.62 ± 1.28 for the BG and 14.15 ± 1.62 for the CG. The mean total symptom score for the PG was 13.93 ± 1.56 (Figure 3). Post-treatment mean symptom scores were 2.77 ± 1.19 for the BG and 2.69 ± 1.86 for the CG. The post-treatment mean symptom score for the PG was 10.87 ± 1.89. The difference between the pre-treatment and the post-treatment mean total

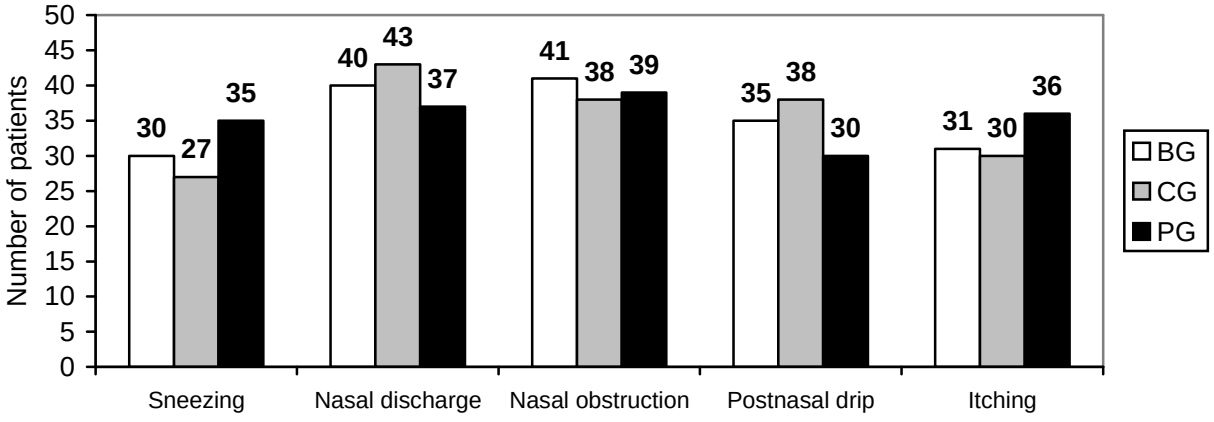

Figure 1. The number of the patients with severe individual symptoms for each study parameter in BG, CG, PG.

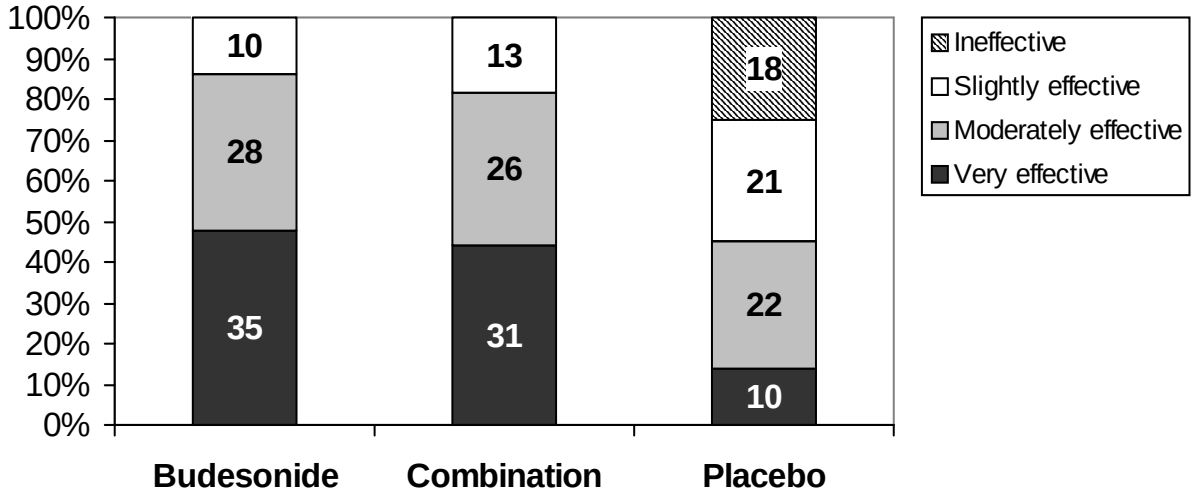

Figure 2. Patients' overall assessments of the treatment.

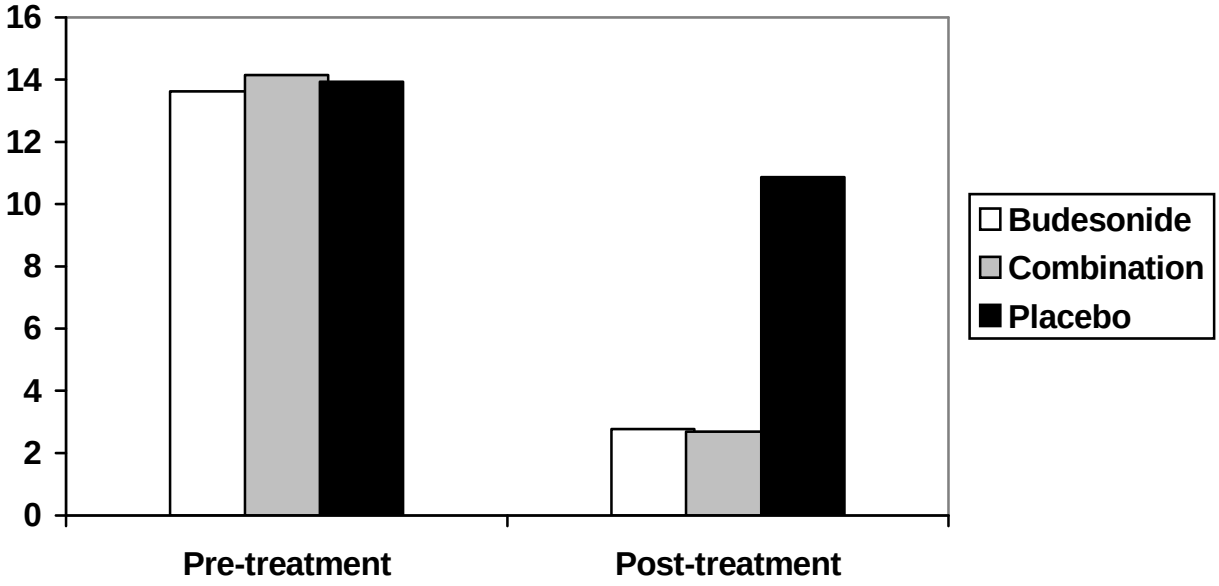

Figure 3. The mean total pre-treatment and post-treatment symptom scores. The difference between the pre-treatment and the post-treatment mean total symptom scores is statistically significant in BG and CG ($p<0.05$).

symptom scores was statistically significant in BG and CG ($p<0.05$) whereas this difference was not significant in the PG ($p>0.05$). The difference between the post-treatment mean total symptom scores of BG and CG was not statistically significant ($p>0.05$). The differences between the post-treatment mean symptom scores of BG-PG and CG-PG were significant ($p<0.05$).

Individual symptoms of seasonal allergic rhinitis: In this part of the study, the efficacy of the treatment regimens on individual symptoms of allergic rhinitis were investigated only on the patients with severe pre-treatment symptom for the studied parameter, i.e. with pre-treatment scores equal to 3. The post-treatment symptom scores of the three groups were compared.

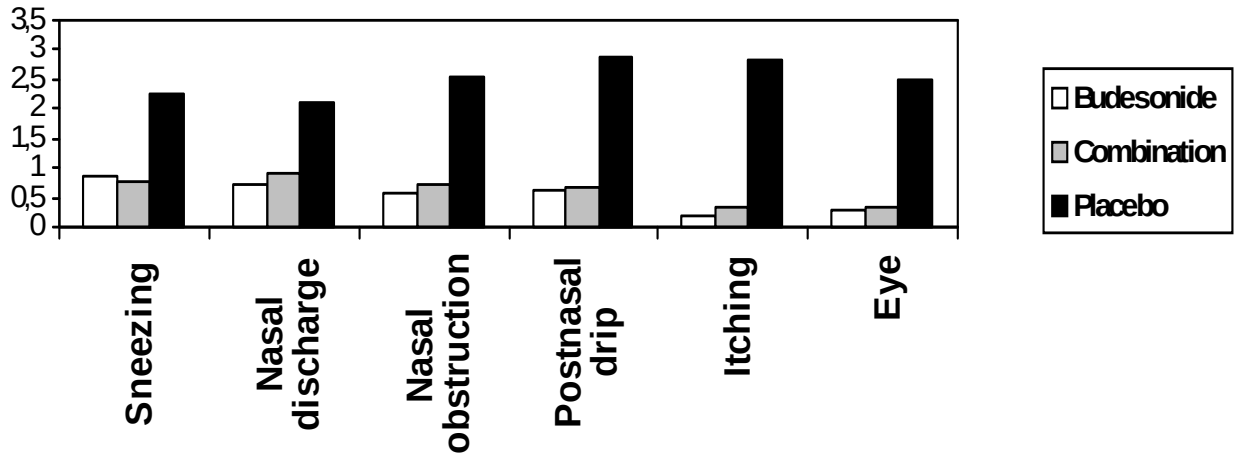

Figure 4. The mean post-treatment symptom scores for individual symptoms. The pre-treatment symptom scores were 3 for all parameters in all groups since only the patients with severe individual symptoms were taken into consideration for this part of the study.

The differences between pre-treatment and post-treatment symptom scores were statistically significant for all individual symptoms (sneezing, nasal discharge, nasal obstruction, postnasal drip, nose/throat itching, and eye symptoms) in both BG and CG ($p<0.05$). These differences were not significant for any studied parameter in the PG ($p>0.05$).

Since only the patients with severe individual symptoms were taken into consideration in this part of the study, the mean pre-treatment symptom scores were 3 for all individual symptoms in all groups. The mean post-treatment symptom scores for the BG, CG and the PG are presented in Figure 4. The differences of the post-treatment symptom scores were not statistically significant for any parameter between the BG and CG ($p>0.05$). The differences were significant for all parameters between CG-PG and BG-PG groups ($p<0.05$).

Three patients with severe, two patients with moderate and four patients with mild eye symptoms (total nine patients; 12.3%) did not benefit from the treatment for their ocular symptoms in the BG. Five patients with mild symptoms and four patients with moderate symptoms (total nine patients; 12.9%) required additional therapy for their ocular symptoms in the CG. Azelastine ophthalmic drop (Allergoftal®) was administered to patients with eye symptoms who did not respond to the treatment protocols.

Sixty-eight patients had edema of the nasal turbinates on their initial examination in the BG. The edema of the turbinates was reduced in 55 of the patients on their control visits (80.8%). This rate was 83.5% in the CG and 23.8% in the PG.

Pulmonary functions: 53 patients in the BG, 58 patients in the CG and 49 patients in the PG had mild or moderate asthma. None of the patients in any study group had severe asthma. The pulmonary functions did not get worse in any patients at the end of the therapy.

Side effects

Nasal dryness in three patients and mild epistaxis in one patient were encountered as side effects in the BG. Nasal dryness in four patients and somnolence in 1 patient were noted in the CG. All of the mentioned side effects were mild and medications were not discontinued. Two patients in the PG complained of somnolence.

Discussion

The results of this study suggest that budesonide alone or in combination with cetirizine is effective for alleviating nasal and ocular symptoms of severe seasonal allergic rhinitis. Both treatment regimens were superior to the placebo.

The goal of pharmacotherapy for allergic rhinitis is to alleviate allergic symptoms without incurring adverse side effects (11). The ideal agent must control all symptoms with a rapid onset of action, be free of side effects, have no drug interactions, and have a low cost. Unfortunately, such an agent is not present. In lieu of increased cost, physicians frequently combine preparations in order to achieve maximum symptom control.

Treatment of patients with severe seasonal allergic rhinitis is a challenging problem. A combination of nasal steroids and antihistamines is recommended for patients with severe symptoms (12). In vitro findings with antihistamines and nasal steroids may suggest a complementary mechanism of action; i.e. there may be a potential inhibition of both mast cell and basophil degranulation, and of cell activation and eosinophil recruitment. If corticosteroids and antihistamines were used concomitantly, this might be translated into additional benefit (13). In fact there are only a few studies in the literature concerning the benefit of combining the nasal steroids with the antihistamines, and none of these studies focuses on patients with severe symptoms.

Simpson compared the efficacy of budesonide and terfenadine separately and in combination on 106 patients with seasonal allergic rhinitis (10). Budesonide alone reduced the mean symptom scores for blocked nose, itchy nose, runny nose and eye symptoms similar to the combination of budesonide and terfenadine. The combination of budesonide and terfenadine reduced the mean sneezing score more than either terfenadine or budesonide alone, the difference being statistically significant.

Ratner et al compared the efficacy of loratadine and fluticasone propionate aqueous nasal spray alone or in combination on 114 patients with seasonal allergic rhinitis (9). They reported that fluticasone and fluticasone+loratadine were more efficient than placebo or loratadine alone. Comparisons of clinician rated nasal symptom scores, overall evaluation symptom scores and ophthalmic symptom scores showed no statistically significant differences between fluticasone and fluticasone+loratadine treatment groups.

Both of these studies do not support the hypothesis that long term concomitant administration of a nasal steroid and an antihistamine may increase the clinical benefit. However, neither of these studies focuses on the patients with severe seasonal allergic rhinitis. Our study focuses on this group of patients.

Patients with severe seasonal allergic rhinitis were included in our study in the pollen season, when their symptoms peaked. The medical therapy was administered for 3 weeks in order to achieve the maximum effect of the medications.

The overall assessment of the therapy was comparable in BG and CG. Both treatment regimens were assessed as “very effective” in 47.9% of the BG and in 44.3% of the CG ($p>0.05$). None of the patients in either group reported the therapy as ineffective. However, only 14.1% of the patients in the PG rated the therapy as very effective. The difference between BG-PG and CG-PG were significant ($p<0.05$).

Budesonide therapy was safe and mild side effects were encountered in 4.8% of the patients. The side effects encountered during the combination therapy were also mild and were encountered in 6.7% of the patients.

Budesonide and the budesonide+cetirizine combination were both significantly effective significantly for alleviating nasal and ocular symptoms of severe seasonal allergic rhinitis. The differences between the mean individual post-treatment symptom scores were not statistically significant between the two groups. The oedema of the turbinates was reduced in 80.8% of the patients in the BG and in 83.5% in the CG, and this result reflects the efficacy of both treatment regimens on nasal obstruction. This rate was 23.8% in the PG. The differences between the BG-PG and CG-PG were significant ($p<0.05$). It was apparent that budesonide alone was as effective as its combination with cetirizine for controlling nasal symptoms of severe allergic rhinitis.

The efficacy of budesonide and budesonide +cetirizine were comparable in patients with severe eye symptoms. Nine patients in BG (6.62%) and

another 9 patients in CG (7.03%) required the addition of topical antihistamine eye drops to control their ocular symptoms. Budesonide and combination regimen were not superior to one another in controlling severe eye symptoms.

Conclusion

Budesonide aqueous nasal spray alone is as effective as its combination with cetirizine tablets for controlling nasal and ocular symptoms of severe seasonal allergic rhinitis and can be used alone for sufficient symptom control with a low incidence of side effects. Instead of concomitant administration budesonide and cetirizine at the beginning of the therapy, initial cost effective therapy of severe seasonal allergic rhinitis may begin with budesonide alone. In case of insufficient response to treatment, instead of adding cetirizine, administration of an additional topical decongestant, ipratropium bromide, antihistamine eye drops or a topical nasal antihistamine may be considered. The benefit of combining these agents with budesonide nasal spray for patients with severe seasonal allergic rhinitis still needs to be investigated.

REFERENCES

1. Spector S L. Overview of comorbid associations of allergic rhinitis. J Allergy Clin Immunol 1997; 99: 773-80.
2. International Rhinitis Working Group. International consensus report on the diagnosis and management of rhinitis. Allergy 1994; 49 Suppl: 10-2.
3. Barnes CL, McKenzie CA, Webster KD, Poinsett-Holmes K. Cetirizine: A new, nonsedating antihistamine. Ann Pharmacother 1993; 27: 464-70.
4. Fireman P. Treatment strategies designed to minimize medical complications of allergic rhinitis. Am J Rhinol 1997; 11: 95-102.
5. Noble SL, Forbes RC, Woodbridge HB. Allergic rhinitis. Am Fam Physician 1995; 51: 837-46.
6. Wang D, Smitz J, Waele MD. Effect of topical applications of budesonide and azelastine on nasal symptoms. Int Arch Allergy Immunol 1997; 114: 185-92.
7. Mansmann HC, Altman RA, Berman BA, Buchman E, Dockhorn RJ, Leese PT, et al. Efficacy and safety of cetirizine therapy in perennial allergic rhinitis. Ann Allergy 1992; 68: 348-51.
8. Mabry RL. Intranasal corticosteroids and cromolyn. Am J Otolaryngol 1993; 14: 295-300.
9. Ratner PH, vanBavel JH, Martin BG, Hampel FC Jr, Howland WC 3rd, Rogenes PR, et al. A comparison of the efficacy of fluticasone propionate aqueous nasal spray and loratidine. J Fam Pract 1998; 47: 118-25.
10. Simpson RJ. Budesonide and terfenadine, separately and in combination, in the treatment of hay fever. Ann Allergy 1994; 73: 497-502.
11. Ferguson BJ. Cost effective pharmacotherapy for allergic rhinitis. Otolaryngol Clin North Am 1998; 31: 91-110.
12. van Cauwenberge P, Bachert C, Passalacqua G, Bousquet J, Canonica GW, Durham SR, et al. Consensus statement on the treatment of allergic rhinitis. Allergy 2000; 55:1-19.
13. Howarth PH. A comparison of the anti-inflamatory properties of intranasal corticosteroids and antihistamines in allergic rhinitis. Allergy 2000; 62: 6-11.

Geliş Tarihi: 22.03.2002

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