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(Continued on page A-6)

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Budesonide and terfenadine, separately and in combination, in the treatment of hay fever

Richard J. Simpson, MB, ChB

Background: While hay fever is a very common experience, its treatment in primary care setting has been little reported in controlled studies.

Objective: This study sought to evaluate the patient's assessment of efficacy of an intranasal steroid spray (budesonide) alone or in combination with an antihistamine (terfenadine) against terfenadine alone or placebo alone.

Methods: A double-blind parallel group, placebo-controlled trial design was used, comparing the four groups. Each group used an active or placebo spray and active or placebo tablets. Symptom scores were recorded daily in diaries over a 21-day period.

Results: Overall assessment of efficacy by the 106 patients was significantly greater ($P < .05$) for budesonide versus terfenadine or placebo alone. There was a 40% placebo response. Budesonide was more effective than terfenadine for all individual symptom scores, particularly nasal blockage, against which terfenadine was ineffective. Adverse effects were mild and transient for all groups.

Conclusions: Budesonide alone is a highly effective treatment for hay fever with few side effects.

INTRODUCTION

It has been estimated that 10% to 17% of North Americans experience allergic rhinitis[1] and that hay fever, an allergy to pollen resulting in rhinitis and conjunctival symptoms, is one of the most common forms of the disease. Following exposure to the allergen, IgE-mediated stimulation of mast cells results in the release of allergy mediators such as histamine, which cause increased vascular permeability, mucous secretion, and stimulation of neural reflexes (resulting in pruritus and sneezing). Late-phase inflammatory reactions[2] include the attraction and infiltration of inflammatory cells, such as mast cells, eosinophils, basophils, neutrophils and lymphocytes into the mucosa.[3] The increased irritability of the nose observed during the allergy season is largely due to this inflammatory reaction. The result of these processes is the characteristic nasal symptoms of hay fever including pruritus, nasal congestion, runny nose, and sneezing.

Treatment of hay fever includes antihistamines, decongestants, sodium cromoglycate,[4] topical (intranasal),[5] or systemic[6] steroids and immunotherapy.[7] Antihistamines are well-established in the treatment of hay fever, reflecting the role of histamine release in its pathogenesis, but their usefulness has until recently been limited because of their anticholinergic, central nervous system and sedative side effects,[8] which are potentiated by sedatives, hypnotics, antidepressants, and alcohol. More recent H_1-receptor antagonists produce a much lower incidence of sedation[8]; however, terfenadine, the most widely prescribed antihistamine, and a second compound in this group, astemizole, have both been shown to cause ventricular arrhythmias in overdose[9,10] or when used in combination with erythromycin or other macrolide antibiotics and the antifungal preparation ketoconazole.[11] Although clinical trials have shown antihistamines to relieve symptoms such as sneezing, itchy nose and runny nose, in general they are not thought to be effective in relieving nasal blockage, and thus may be formulated in combination with a decongestant.[12]

Systemic treatment with corticosteroids can be used in hay fever, but is usually reserved for the most severe and persistent cases because of the risk of adverse effects associated with the long-term use of this type of therapy.[13] Intranasal corticosteroids, on the other hand, provide one of the most potent therapies for hayfever[7,14] and their local mode of application avoids the adverse effects associated with systemic corticosteroids while at least equalling their efficacy.[15] They also lack the sedative effects of antihistamines. The limitations of intranasally applied steroids are that, due to their localized action, they may not be effective in controlling eye symptoms and that some patients experience nasal irritation or mild epistaxis as a result of using them.[16]

In the current study, the efficacy of intranasal budesonide, a corticosteroid preparation, was compared with that of terfenadine and a combination of the two in the treatment of hay fever, in a double-blind, parallel-group, placebo-controlled study.

MATERIALS AND METHODS

Patients

Men and women aged 15 years or

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over at entry were recruited from a primary care setting into the trial. All patients had experienced symptoms of hay fever between May 1 and August 31 for at least 2 years preceding the study, and at the time of recruitment were suffering from two or more of the following symptoms: blocked nose, runny nose, itching nose, or sneezing. Any patients who were taking oral corticosteroids, were suffering from respiratory tract infections (bacterial, viral, or fungal) at the time of recruitment, had taken desensitization therapy during the previous 12 months or who suffered hay fever symptoms outside the specified period were excluded from the study, as were pregnant women.

The nature and purpose of the study were explained to the patients in both oral and written form, and their written consent to participation in the study was obtained. The study was approved by the local ethics committee and was performed in accordance with the Declaration of Helsinki.

Study Procedures

Patients visited their general practitioner on entry to the study, at which time demographic details and the patient's assessment of hay fever symptoms during the previous 24 hours were recorded. The symptoms assessed were blocked nose, runny nose, itchy nose, sneezing bouts, runny eyes, and sore eyes. Symptoms were scored using a 4-point system where 0 = no symptoms, 1 = mild symptoms (present but not troublesome), 2 = moderate symptoms (some discomfort experienced), and 3 = severe symptoms (discomfort experienced during most of the waking hours). A minimum score of 2 was required for entry into the study.

On entry to the study, patients were randomized to one of four parallel groups receiving (1) intranasal budesonide (Rhinocort, Astra Draco AB, Lund, Sweden), 200 μg bid, plus terfenadine (Triludan, Marion Merrell Dow, Uxbridge, Middlesex, UK), 60 mg bid; (2) terfenadine, 60 mg bid, plus a placebo nasal spray (identical to the budesonide nasal spray but delivering propellant and lubricant only); (3) intranasal budesonide, 200 μg bid, plus placebo tablets identical in appearance to the terfenadine tablets; and (4) placebo nasal spray plus placebo tablets. Patients were instructed to deliver two puffs from the nasal spray into each nostril morning and evening, and to take one tablet in the morning and one in the evening, for 21 days. The use of other medications for hay fever, particularly oral corticosteroids and antihistamines, was forbidden but in the event of troublesome eye symptoms patients were permitted to use xylometazoline or metazoline eye drops.

Patients were supplied with diary booklets and asked to record, at the end of each day, symptom scores experienced during the day for blocked nose, runny nose, sneezing, itchy nose, runny eyes and sore eyes, using the same scoring system as on entry to the study. The number of eye drops used during each 24 hours was also recorded, as were any comments about the symptoms or treatment.

Patients visited their general practitioner after seven days' treatment, and were reminded of their option to withdraw from the study if the previous week's treatment had been ineffective. The diary booklets were checked for accuracy and completeness, and any comments made by the patients were recorded. At the final visit, after 21 days of treatment, comments by either the patient or the physician were recorded, any inconsistencies in the diary booklets clarified, and patients were asked to make a global assessment of the efficacy of treatment according to a 4-point scale where 0 = ineffective, 1 = slightly effective, 2 = noticeably effective, and 3 = very effective.

Statistical Analysis

Mean weekly symptom scores for each patient who completed the study were determined from the diary booklets and overall means for each treatment group calculated from these. One-way analysis of variance (using pooled variance) was carried out on the 3-week treatment mean, the last week of treatment and weeks 1, 2, and 3 separately. Where statistically significant treatment differences were indicated by the F-ratio, linear contrasts were used to determine the statistical significance of individual treatment differences.

Global assessment and eye drop use were subjected to Kruskal-Wallis one-way analysis of variance followed by the Wilcoxon rank sum-W test where appropriate.

RESULTS

Efficacy

One hundred forty-three patients reporting to their general practitioner with symptoms of hay fever were recruited into the study. Records from six patients were unusable because of confused numbering (five patients) and lost data (one patient). Twenty patients withdrew because of lack of treatment efficacy, the majority of these (12) being in the placebo group A further three patients withdrew as a result of adverse events and five patients failed to return for assessment on one or more occasions. Three patients severely violated the protocol during the trial, and were withdrawn. Table 1 shows demographic characteristics and symptom severity at baseline for the 106 patients who were evaluated for efficacy. On entry to the study, the four treatment groups were well matched with respect to symptom severity and demographic characteristics, with the exception of the placebo group which had a higher proportion of men than the other groups.

Figure 1 shows the results of the patients' overall assessment of the efficacy of treatment, whereas Figure 2 shows the analysis of individual symptom scores derived from

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