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Original Article

Effect of pre-seasonal and seasonal treatment with budesonide topical nasal powder in patients with seasonal allergic rhinitis

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ABSTRACT

The efficacy and safety of budesonide nasal powder (Rhinocort Turbuhaler®) in seasonal allergic rhinitis when given only at the onset of symptoms during the pollen season or when also given before the pollen season, were compared. The study was carried out in 364 patients from 14 centres in Italy as a randomized, double-blind, parallel-group, placebo-controlled comparison of five alternative treatment regimens given for 4 weeks during the pre-pollen and early pollen season (PPS) and for 6 weeks during the pollen season (PS). It was concluded that either 200 μg or 400 μg of budesonide given once daily PPS provides significant control of symptoms experienced during PPS. The 400 μg dose, however, also provides additional prophylactic protection against symptoms during early PS. When the pollen season is established, the dose of budesonide may be reduced to 200 μg.

Key words: allergic, budesonide, inflammation, prophylactic, rhinitis, seasonal, steroids

INTRODUCTION

Allergic rhinitis, the most common form of atopic disease, is characterized by inflammation of the nasal mucosa, resulting in symptoms such as sneezing, hypersecretion and nasal blockage. Cytology of the nasal mucosa in such patients indicates that eosinophils, neutrophils and basophils are present.[1] An influx of these cells accompanies the late reaction in response to nasal allergen challenge and there is a strong correlation between the number of basophils and the level of histamine. There is also a correlation between the number of eosinophils and the level of eosinophil major basic protein, suggesting that the inflammatory cells not only enter the nose, but also degranulate,[2,3] thereby releasing inflammatory mediators.

Topical glucocorticosteroids such as budesonide have been shown to be highly effective and safe for the treatment of allergic rhinitis, providing at least comparable efficacy to that of oral steroids, with reduced systemic side-effects.[4] If patients are treated for 1 week with budesonide during a pollen-free period, the immediate response provoked by subsequent challenge is markedly reduced,[5] probably because topical corticosteroids improve the nasal epithelial barrier and inhibit the influx of inflammatory cells in response to allergens.[6] Budesonide has been shown to reduce the influx of eosinophils and the level of eosinophilic cationic protein (ECP),[7] as well as tissue levels of histamine.[8] This has also been demonstrated with fluticasone propionate, and a statistical correlation was found between the degree of improvement in nasal reactivity to histamine and the reduction in ECP levels in the nasal lavages.[9]

Inhaled budesonide is capable of inhibiting the late response to allergen challenge, even when it is given immediately prior to challenge, whereas the immediate response is only inhibited after some days of pre-treatment.[10] These results indicate that steroids are acting on different mechanisms according to treatment duration. Some markers of nasal mucosal inflammation indicate that the inflammatory process may be active during the allergy season before any symptoms appear,[11,12] so it is probably better to pre-treat patients for some weeks prior to the main pollen season. With this in mind, the aim of this study was to compare the efficacy of budesonide administered for 1 month before (i.e. prophylactically) as well as during the pollen season, with that administered only during the pollen season.

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METHODS

Patients

Patients aged 15–65 years were eligible for the study if they had a history of seasonal allergic rhinitis (to grass pollen) of at least 1 year and fulfilled the following additional criteria: no infectious, atrophic or perennial rhinitis; no acute or chronic sinusitis; no nasal polyposis; no asthma requiring corticosteroid treatment; no systemic corticosteroid therapy during the previous month; no current immunotherapy; no pregnancy or lactation. They were recruited from 14 clinics throughout Italy and entered the study on suitable starting dates between March and May 1992, which were estimated to be in the pre-pollen season (PPS) for each region according to the mean pollen count data previously reported by the Italian Aeroallergen Network.[13]

Study design and assessments

The study was conducted over a 10 week period; 4 weeks before the expected pollen season and 6 weeks during the pollen season. Patients attended the clinic on four occasions: at entry (visit 1), after 4 weeks (visit 2), 7 weeks (visit 3) and 10 weeks (visit 4). At entry, their demographic details were recorded and a skin prick test was performed for allergy assessment, if one had not been done recently.

Patients were then randomly allocated to one of five parallel treatment regimens. Treatment was administered in a double-blind fashion using identical nasal inhalers (Turbuhaler®) that contained either lactose (placebo) or budesonide, 100 μg/dose or 200 μg/dose delivered as a pure powder.[14] Patients were treated for 4 weeks before the expected (pre-) pollen season (PPS) and for 6 weeks during the pollen season (PS; Table 1).

Patients were asked to take their treatment (one dose to each nostril) at the same time each morning and were permitted to take 'rescue' antihistamine therapy, if their symptoms persisted despite regular intake of their study drug. Their use of extra medication was to be recorded in a daily diary card, as were the symptoms of blocked nose, runny nose and sneezing. The symptoms were rated on a scale from zero to 3; (0=no symptoms; 1=mild symptoms, present but not troublesome; 2=moderate symptoms, frequently troublesome but not sufficient to interfere with normal daily activity or night-time sleep; 3=severe symptoms, sufficiently troublesome to interfere with normal daily activity or night-time sleep). At subsequent visits, patients were asked whether their treatment had controlled their symptoms.

Table 1. Treatment regimens given during the pre-pollen and early pollen season (PPS) and during the pollen season (PS)

Group	Pre-pollen and early pollen season	Pollen season
A	Budesonide 400 μg once daily	Budesonide 200 μg once daily
B	Placebo once daily	Budesonide 400 μg once daily
C	Budesonide 400 μg once daily	Budesonide 400 μg once daily
D	Budesonide 200 μg once daily	Budesonide 200 μg once daily
E	Placebo once daily	Budesonide 200 μg once daily

Pollen counts

Data on daily pollen counts were obtained from the Italian Aeroallergen Network, which uses the Burkard volumetric trap method for pollen collection at sampling sites all over Italy (Fig. 1). The number of grass pollen grains were reported as the number of grains/cubic meter of air, and the total number of patient exposure days (study duration days × number of centres) to the different pollen levels of Graminaceae and Parietaria are shown in Fig. 2.

Statistical methods

Data were analyzed using an 'all patients treated' approach, in which patients had to have taken at least one dose of medication and have at least 3 days of diary data. Unlike the 'per pro-

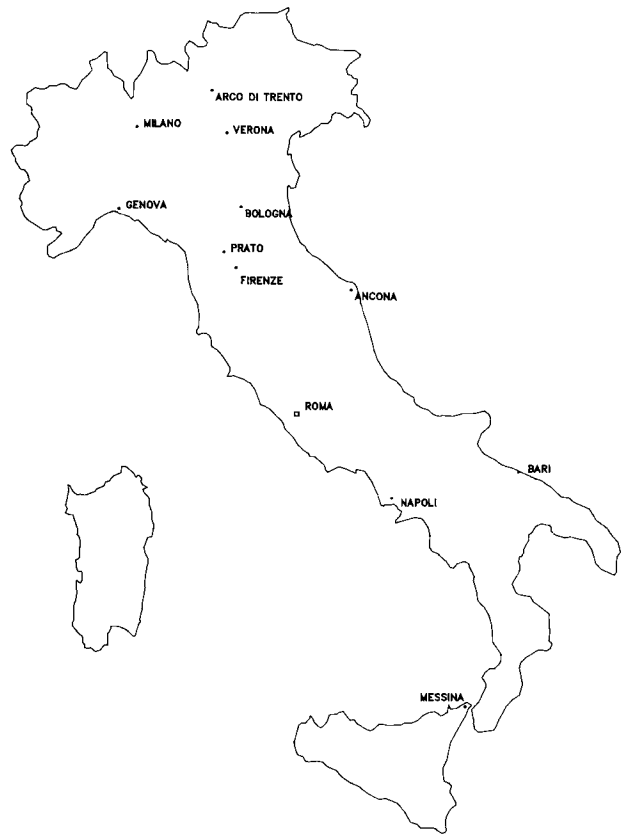

Fig. 1 Pollen sampling sites used by the Italian Aeroallergen Network.

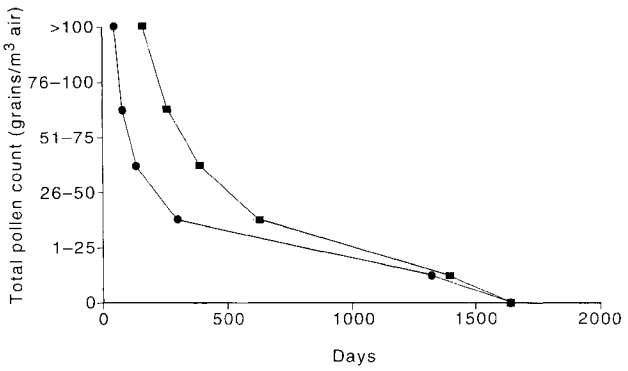

Fig. 2 Total exposure to *Graminaceae* (●) or *Parietaria* (■) pollens (total pollen counts) throughout the study. Days, study duration days × number of centers.

tocol' approach, this analysis included data from the diary cards for days on which additional decongestants et cetera had been taken by the patients. It was evident from the data that such days represented symptomatic days and should thus be included in the analysis.

The primary efficacy variables were the three nasal symptoms recorded in the daily diary and the patient's assessment of the study treatment at the end of the study. For each patient, mean values were calculated for individual symptom scores as well as a total nasal symptom score for the 4 weeks pre-pollen season, individual weeks 1, 2 and 3 of the pollen season and weeks 4–6 combined. Analysis of covariance (ANCOVA) was used to test for differences among the five treatment groups (checking for parallelism) and, if the overall treatment difference was significant, pairwise comparisons of the treatment groups were investigated to find out where the differences were. The mean Graminaceae counts corresponding to each patient's treatment period were included in the analysis as a covariate, to adjust for any biases that might have resulted from group differences in mean pollen levels. To investigate the effect of treatment in relation to the level of pollen, the pollen count interval method of Wilkinson and Taudorf[15] was used. Each patient's daily pollen level was the corresponding level of Graminaceae, Parietaria, or both, according to the patient's sensitivity. The range of pollen counts was divided as closely as possible into quartiles so that each of the four intervals contained a similar number of days. This was done for PPS and PS. The total symptom scores were analyzed for each pollen interval using analysis of variance (ANOVA).

The patient's own assessment of treatment recorded at visits 2, 3 and 4 was compared for the five treatment groups using the Kruskal–Wallis one-way ANOVA by ranks. When the test resulted in significance, pairwise comparisons of the treatment groups were made.[16]

Antihistamine consumption was calculated as the number of days per week on which antihistamines were taken. This was then compared across the treatments for the PPS and the PS, using ANCOVA (including mean Graminaceae counts as a covariate).

Results

Patients included

A total of 364 patients were randomized to study treatment, 219 males and 145 females with a mean age of 30.7 years (range 14–67 years). All had a history of at least one season of grass pollen-induced allergic rhinitis and 58% of the patients had had rhinitis for more than 5 years. Skin prick tests indicated that 247 patients (68%) were positive to Graminaceae, 32 (9%) to Parietaria and 85 (23%) were positive to both Graminaceae and Parietaria.

In general, the five treatment groups were comparable initially, although there were more females in groups C and D. Demographic and disease status details are summarized for each treatment group in Table 2.

Efficacy

Data were available from 345 patients for an 'all patients treated' analysis. The remaining 19 recruited patients were excluded from the analysis due to paucity of diary card data (17 patients) or no treatment (2 patients). Mean daily symptom scores for sneezing, blocked nose and nasal secretion are presented in Table 3. During the PPS, significant treatment differences were detected for sneezing ($P=0.001$) and nasal secretion ($P=0.0001$). Pairwise comparisons of the treatment groups indicated that both sneezing and nasal secretion were significantly lower during treatment with 400 μg or 200 μg budesonide compared with the placebo. No significant differences were noted for blocked nose. During the PS, significant treatment differences were detected during the first week only for nasal secretion ($P=0.0037$). Pairwise comparisons indicated

Table 2. Demographic and disease details

	Treatment group				
	A	B	C	D	E
n	72	72	73	73	74
Males/females	52/20	45/27	34/39	38/35	50/24
Mean age (years)	32	31	31	30	31
Mean weight (kg)	70	67	67	67	68
Mean height (cm)	173	170	169	170	172
Smokers (%)	14	18	15	16	14
Duration of rhinitis					
1–2 years	10	11	8	9	12
>2 years	62	61	65	64	62
Allergic to					
Graminaceae	50	47	49	52	49
Parietaria	8	8	6	1	9
Graminaceae + Parietaria	14	17	18	20	16

Table 3. Mean daily symptom scores (adjusted for pollen level)

	Treatment group				
	A 400 μg +200 μg	B Placebo +400 μg	C 400 μg +400 μg	D 200 μg +200 μg	E Placebo +200 μg
Sneezing					
PPS	0.348	0.591	0.372	0.398	0.619
PS week 1	0.418	0.662	0.498	0.547	0.643
PS week 2	0.525	0.513	0.564	0.701	0.685
PS week 3	0.543	0.519	0.557	0.726	0.735
PS weeks 4–6	0.433	0.399	0.443	0.418	0.409
Nasal secretion					
PPS	0.312	0.663	0.336	0.469	0.747
PS week 1	0.361	0.746	0.430	0.567	0.670
PS week 2	0.466	0.594	0.578	0.706	0.657
PS week 3	0.532	0.546	0.610	0.709	0.726
PS weeks 4–6	0.439	0.458	0.469	0.446	0.476
Blocked nose					
PPS	0.304	0.519	0.376	0.420	0.536
PS week 1	0.352	0.555	0.415	0.572	0.494
PS week 2	0.425	0.480	0.490	0.590	0.508
PS week 3	0.436	0.500	0.560	0.609	0.587
PS weeks 4–6	0.441	0.392	0.372	0.382	0.423

PPS, pre-pollen and early pollen season; PS, pollen season.

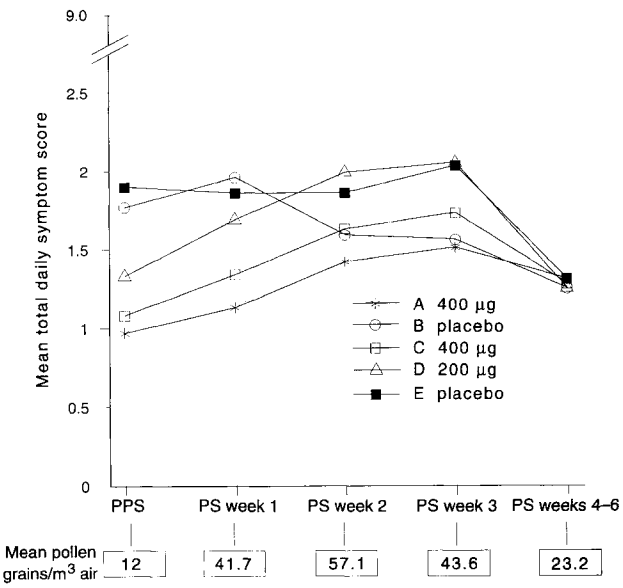

Fig. 3 Mean total daily symptoms for each treatment group during each treatment period. The mean pollen level for each treatment period is boxed. PPS, pre-pollen season and early pollen season; PS, pollen season.

that petients treated with 400 μg budesonide during PPS were significantly better controlled than those treated with placebo during PPS and during the first week of PS, irrespective of treatment given during PS.

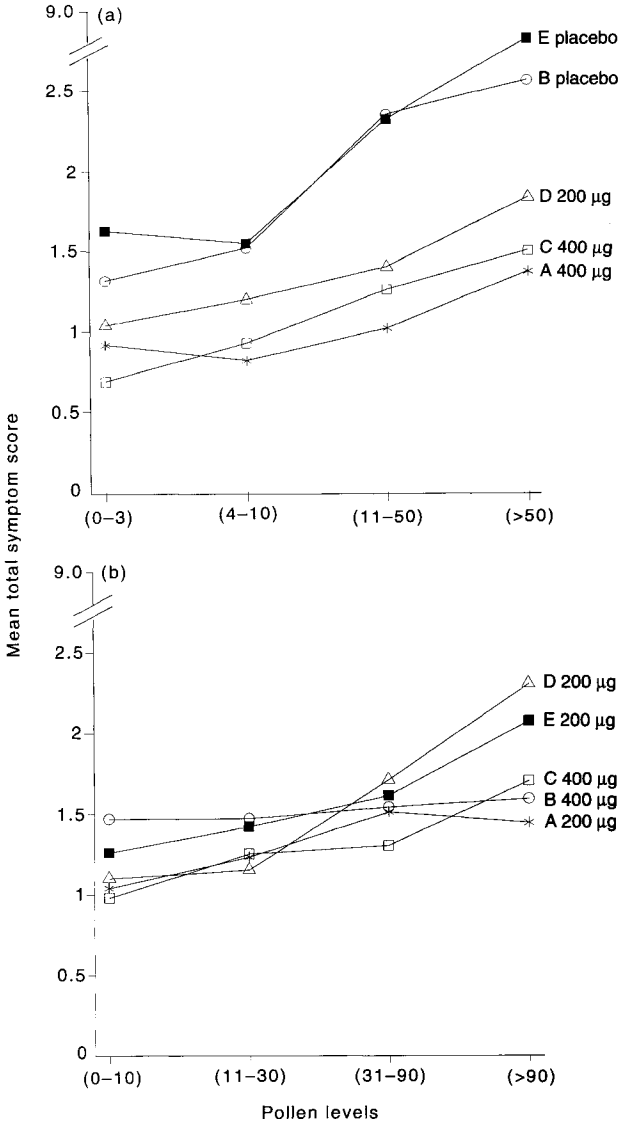

Fig. 4 Mean total symptom scores presented according to quartile pollen levels during (a) pre-pollen season and (b) pollen season.

Mean total daily symptom scores are shown in Fig. 3 for each treatment group across each treatment period. The means have been adjusted for pollen levels on an individual patient basis. Mean pollen levels for the group during each treatment period are also indicated in Fig. 3 under the appropriate time interval. During the pre-pollen period, significant treatment differences were detected using ANCOVA ($P=0.0003$). Pairwise comparisons indicated that the total symptom score was significantly lower during treatment with 200 μg or 400 μg budesonide compared with the placebo. During the PS, a significant treatment difference was detected during the first week only, with evidence that 400 μg budesonide was significantly more effective than the placebo in controlling symptoms. Mean total symptom scores are presented according to quartile pollen levels for PPS and PS

in Figs 4a and 4b, respectively. At pollen levels of up to 10 grains/m^3 air during PPS, total symptom scores were significantly lower on budesonide 400 μg compared with the placebo. At levels of 10–50 grains/m^3 air, symptoms were significantly lower on both 200 μg and 400 μg budesonide compared with the placebo, while at levels of > 50 grains/m^3 air, only the 400 μg dose of budesonide was significantly better than the placebo. During the entire PS, where all treatments were active, no significant difference was detected between 200 μg and 400 μg budesonide in terms of total symptom control at any of the pollen levels.

Patient assessment

When asked at the clinic about their symptom control, patients who had taken either 200 μg or 400 μg budesonide PPS reported significantly better symptom control than those who had taken the placebo ($P=0.0001$) and they also consumed significantly less antihistamine ($P=0.03$). During PS, no difference in symptom control and no difference in anthistamine consumption were noted between the two doses of budesonide.

Tolerability

Safety profiles were similar for all groups, with adverse events being generally mild and well-tolerated. Three patients discontinued study treatment due to an adverse event. During PPS, one patient discontinued treatment with 200 μg budesonide at his own request due to moderate peri-orbital monolateral oedema and one patient discontinued budesonide 400 μg due to mild urticaria. During PS, one patient had severe rhinitis and sneezing after inhalation of 200 μg budesonide. All patients made a full recovery after stopping treatment. There were no serious adverse events during the study.

Discussion

Previous studies have shown that preventative or prophylactic treatment with budesonide[10] or other inhaled corticosteroids such as beclomethasone dipropionate[17] and fluticasone propionate[18] is more effective if treatment is initiated at least 1 week prior to allergen challenge. In this placebo-controlled study, an attempt was made to evaluate budesonide treatment given for 1 month prior to the start of the pollen season. There were, however, practical difficulties in recruiting so many patients to the study at one time. To allow for the variation in the pollen levels during the PPS treatment period, the results were calculated taking the daily pollen level of exposure for each individual patient into account in the analysis. This should give a more accurate reflection of the true treatment efficacy in controlling symptoms. Patients who received placebo PPS (groups B and E) had scores for individual symptoms that were approximately twice those of the budesonide-treated groups. This would appear to indicate that symptoms are already troublesome just before and very early on in the pollen season and would confirm the well-recognized nasal 'priming' effect of the first pollen exposure.[19,20] The 200 μg and 400 μg doses of budesonide were both associated with significant improvement in symptoms compared with the placebo, during PPS. The nasal symptoms experienced in the PPS were well-correlated with pollen levels and total symptom scores were significantly lower during budesonide treatment at all pollen levels (Fig. 2). When patients were asked to assess their treatment at the end of PPS, it was clear that those who had received 400 μg budesonide perceived significant benefit compared with those on the placebo. The beneficial effect of budesonide on symptoms was particularly noticeable at higher pollen levels.

At the beginning of the pollen season itself, patients on 200 μg of budesonide were better controlled if they had been pre-treated with budesonide 400 μg PPS (group A) than those pre-treated with 200 μg PPS (group D). Otherwise, there were no differences between 200 μg and 400 μg. Therefore, once control of symptoms has been established with the 400 μg dose of budesonide PPS, it is possible to maintain the status quo during the pollen season when the dose is reduced to 200 μg. This suggests that it is preferable to pre-treat with a full dose of inhaled corticosteroid in an attempt to stall the inflammatory process in its early stages and reduce the 'nasal priming' effect of the initial pollen challenge.

Budesonide has previously been shown to reduce total symptom scores at all levels of pollen exposure.[21] It is interesting to note from our study that patients in group B, who had received only placebo PPS, obtained good symptom control even at high pollen levels (>90 grains/m^3 air) during PS, while taking 400 μg budesonide; perhaps because the highest pollen levels did not coincide with the start of active treatment. However, the same patients did not have good symptom control at levels of pollen above 10 grains/m^3 air while taking the placebo during PPS. Thus, although the full dose of budesonide is highly effective even when initiated at the start of or during the pollen season, symptoms may be troublesome before the season is fully established.

Topical corticosteroids are thought to have wide-ranging actions within the nose. They seem to act on all aspects of the nasal inflammatory response that have been studied.[22] Their ability to reduce or prevent the influx of inflammatory cells into the nasal mucosa in response to nasal challenge with pollen allergen has been demonstrated both under laboratory conditions[2,7] and during natural pollen exposure during the pollen season.[23,24] They also prevent allergen-induced release of mediators from inflammatory cells[25] and exudation of plasma and plasma-derived mediators from the nasal mucosa.[26] Topical budesonide therapy is considered to be one of the most effective inhaled corticosteroid treatments currently available for allergic rhinitis, its efficacy exceeding that of antihistamines,[27,28] sodium cromoglycate[29] and immunotherapy.[30]

In conclusion, we suggest that the most effective treatment regimen to avoid the troublesome nasal symptoms resulting from pollen allergy, is pre-treatment of patients about 4 weeks prior to, or early in, the pollen season with full-dose topical nasal budesonide (400 μg) or another corticosteroid. After this initial treatment, most patients can be adequately controlled on 200 μg budesonide for the duration of the pollen season.

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