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A comparison of budesonide nasal dry powder with fluticasone propionate aqueous nasal spray in patients with perennial allergic rhinitis*

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SUMMARY

There is circumstantial evidence that the incidence of allergic rhinitis is becoming increasingly common. There may also be a need for more potent drugs with minimal local and systemic side effects. This study has compared the efficacy and safety of budesonide delivered as nasal dry powder with fluticasone propionate aqueous nasal spray in the treatment of perennial allergic rhinitis. Ninety-eight patients participated in a randomized, parallel group and partly blinded study. Treatment consisted of budesonide dry powder (Rhinocort® Turbuhaler®) at once daily doses of 200 µg (n=24) or 400 µg (n=22), fluticasone propionate (200 µg) once daily (n=25), and placebo for budesonide dry powder (n=27). A six-week treatment period was preceded by a two-week baseline period without treatment. Efficacy was assessed by daily subjective scoring of nasal symptoms. Safety was assessed by rhinoscopy, analysis of urine cortisol, and questioning of adverse events. All active treatments were significantly superior to placebo in controlling nasal symptoms. No significant differences in efficacy were found between the two budesonide regimens and fluticasone propionate. Adverse events were few and minor, and non-significantly distributed between treatments. In conclusion, this study shows that budesonide dry powder administered from Turbuhaler® (200 or 400 µg) and fluticasone propionate aqueous spray (200 µg) administered in once daily doses, are effective and safe treatments of perennial allergic rhinitis. These novel treatments may enhance the current available alternatives in clinical practice.

Key words: perennial allergic rhinitis, budesonide, fluticasone, Turbuhaler

INTRODUCTION

Allergic disorders of the upper and lower airways have been becoming increasingly common during the past 20 years (Varonier et al., 1984; Aberg, 1989). Asthma is the most serious, but allergic rhinitis surely the most common allergy of the airways (Smith Montgomery and Knowler, 1965). It also seems that the development of allergic rhinitis in some but not all cases may precede asthma (Broder et al., 1974). Allergic rhinitis may indeed be a risk factor in developing asthma. This is further suggested by the common association of allergic rhinitis with bronchial hyperreactivity (Cockcroft et al., 1977). Recent data also suggest that when allergic patients are well treated for their nasal symptoms, the asthma symptoms may decrease (Reed et al., 1988; Corren et al., 1992).

Since the introduction of glucocorticoids for local treatment of allergic rhinitis their effect is well known. However, improvement of topical glucocorticosteroids may be beneficial. This could include drugs that are free of lubricants and preservatives as well as drugs with minimal systemic effects. Budesonide delivered as dry powder in a sniff-actuated device (Rhinocort® Turbuhaler®) is now available for treatment of rhinitis (Pedersen et al., 1991). Major advantages of the dry preparation

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are the absence of interfering excipients, no risk for allergic reactions from preservatives, and effective drug distribution due to the sniff-actuation technique (Thorsson et al., 1993). Fluticasone propionate is a new potent glucocorticosteroid for topical application. It has documented strong anti-inflammatory properties, and a very low bioavailability, at least when absorbed from the gut. This has been suggested to contribute to a higher therapeutical index compared to other topical corticosteroids (Phillips, 1990; Harding, 1990). At present no studies have been reported in the literature that have compared budesonide and fluticasone propionate in the treatment of allergic rhinitis.

The aim of the present study was to compare the efficacy and safety of budesonide delivered as nasal dry powder (Rhinocort® Turbuhaler®) with fluticasone propionate aqueous nasal spray (Flutide Nasal, Swedish trademark) for the treatment of perennial allergic rhinitis.

PATIENTS AND METHODS

Study design

The study was performed with a multi-centre, randomized, parallel-group design. The study was double-blinded with respect to budesonide dry powder (Rhinocort® Turbuhaler®) and placebo, and single-blinded with respect to fluticasone propionate (Flutide Nasal®). A six-week treatment period was preceded by a two-week baseline period without any treatment. The study was performed in accordance with the principles stated in the Declaration of Helsinki and approved by the Local Ethics Committees.

Patients

Ninety-eight adult patients participated. They all had a positive skin prick test or RAST reaction to a relevant allergen (Tables 1-2), performed within one year prior to inclusion. In order to be included the patients must also have had four days of at least moderate nasal symptoms (score=2) during the two-week baseline period. Except for their allergic disease all patients were considered healthy. Further exclusion criteria were active infections, pregnancy, lactation, and structural abnormalities in the nose. No other interfering therapies were allowed during the study.

Treatment

Four treatment groups received the following regimens: once daily in the morning administration of 200 µg from Turbuhaler®, budesonide (400 µg) from Turbuhaler®, fluticasone propionate (200 µg) from aqueous spray bottle, and placebo for budesonide from Turbuhaler®. Throughout the study concomittant medication with terfenadine (Teldanex®, 60-mg tablets) or antazoline/naphazoline (Antasten®-Privin eye drops) for alleviation of troublesome symptoms was allowed.

Efficacy and safety assessment

Treatment efficacy was assessed by the patients' daily subjective scoring of blocked nose, runny nose, sneezing and eye symptoms on a scale from 0 to 3. At the last clinic visit the patients scored the ability of the test medication to control symptoms on a scale from 0-4. Treatment safety was documented at each of the four clinic visits by anterior rhinoscopy. For safety reasons possible influence on the hypothalamo-pituitary-adrenal axis was assessed at the second and fourth clinic visits by measuring 24-h urinary cortisol. Urine cortisol was measured by a gas chromatography and mass spectrometry technique. Occurrence of adverse events during treatment was assessed by the investigators' interrogations at each clinic visit.

Table 1. Patient demographics.

	budesonide 200 µg	budesonide 400 µg	fluticasone propionate 200 µg	placebo for budesonide
patients male/female	24	22	25	27
age (years)	35.1	36.5	36.5	35.3
duration of rhinitis (years)	7.7	6.5	8.3	8.4

Table 2. Type of allergies.

	fluticasone	budesonide 400 µg	budesonide 200 µg	placebo	total
house dust mite	23	15	18	18	74
animal dander	13	9	11	11	44
pollen	2	8	11	11	18
mould	3	1	1	2	7

Compliance

The use of test medication during the treatment period was recorded as the number of doses left in the budesonide- and placebo-treated groups. In the fluticasone propionate group the number of doses was estimated by weighing the spray bottles before and after treatment. The percentage of compliance (defined as the ratio amount used: amount prescribed) was compared between the groups.

Statistics

Statistical evaluations of mean subjective symptom scores and overall treatment efficacy at the end of the study were performed with an analysis of variance (ANOVA), followed by pair-wise comparisons. Two-tailed alternatives were used, where $p < 0.05$ was considered as statistically significant. Global assessment of treatment efficacy (at the end of study), weekly consumption of anti-histamines and change in laboratory findings from baseline were analysed with ANOVA on ranked values.

RESULTS

Of the 98 patients included in the study, one patient in the 400-µg budesonide group discontinued the study, due to common cold. One patient in the 200-µg budesonide group and one in the placebo group withdrew due to deterioration of the disease. One patient in the fluticasone group discontinued the study because of personal reasons. No clinically significant

findings were found during rhinoscopy compared to the baseline period and between all treatment groups.

All active treatments were significantly superior to placebo in alleviating subjective nasal symptoms. No statistical significances between the active treatments were found. When the subjective symptoms scores were calculated over the 2-week baseline and 6-week treatment period, both the budesonide groups and the fluticasone propionate group improved some of their nasal symptoms. This is outlined in Table 3. When the three nasal symptoms were added to a combined nasal symptom score the reduction was significant for all active treatments ($p < 0.01$ for both budesonide groups, and $p < 0.05$ for fluticasone) as compared to placebo (Figure 1). No effect of the active treatments was seen on the eye symptoms. This was true also when changes from baseline for the eye symptoms was evaluated.

A majority of the patients on 400 μg budesonide (57.2%; n=12) experienced substantial or total control of their symptoms. The corresponding figures for other treatments were: 200 μg budesonide: 43.4% (n=10); 200 μg fluticasone propionate: 41.6% (n=10); and placebo: 18.5% (n=5). This revealed a significant difference between all active treatments and placebo (all $p < 0.01$). There was a reduction in the use of terfenadine tablets during the treatment period as compared to baseline for all active treatments, which reached a statistical significance for the budesonide (400 μg) group ($p < 0.05$).

Table 3. Change from baseline in nasal symptoms.

		mean±SD	StD	p-value
blocked nose	bude 400	-0.49	0.54	0.0003
	bude 200	-0.43	0.50	0.0003
	flut 200	-0.40	0.55	0.0017
	placebo	-0.04	0.59	0.76
runny nose	bude 400	-0.32	0.44	0.0028
	bude 200	-0.17	0.34	0.018
	flut 200	-0.15	0.41	0.08
	placebo	-0.09	0.45	0.33
sneezing	bude 400	-0.15	0.39	0.09
	bude 200	-0.41	0.42	<0.0001
	flut 200	-0.26	0.28	0.0002
	placebo	-0.08	0.43	0.37

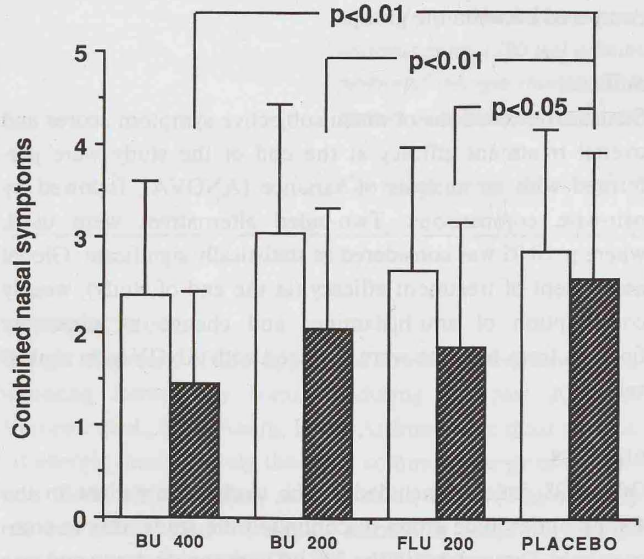

Figure 1. Mean values (±SD) during the baseline and treatment period for combined nasal symptoms. Open bars: baseline period; filled bars: treatment period. P-values refer to changes from baseline for each treatment compared to changes from baseline for placebo treatment.

The 24-h urine cortisol levels did not change significantly between the treatment and baseline periods, and no differences between the treatment groups were found. The creatinine values were indicative of stable renal conditions or good compliance with respect to 24-h urine sampling in all treatment groups.

The mean percentage of compliance ranged between 89.6 (fluticasone); 98.3 (budesonide 400 μg), and 111.2 (budesonide 200 μg). The differences between treatments were statistically not significant.

DISCU5SSION

Recent decades have witnessed an increasing understanding of the pathophysiology of allergic rhinitis and asthma. The pathophysiological changes include an increased number of inflammatory cells and signs of cell activation and plasma exudation. Furthermore, treatment with topical glucocorticoids have effectively improved nasal symptoms and reduced inflammatory indices (Klementsson et al., 1991; Svensson et al., 1990; Brattsand et al., 19). During the last years there is circumstantial evidence that allergic airway diseases are becoming increasingly common. Recent data may also indicate that topical steroid treatment may not only affect the local inflammatory disease in the nasal mucosa, but also reduces circulating-IgE levels (Naclerio et al., 1991). Hence, topical steroid treatment of allergic airway disease seems very appropriate. Although local and systemic side effects are few with the current topical glucocorticoids, there may still be a need for improvement of these treatment regimens. There is also a need to investigate whether any differences in the treatment effects will occur using newer devices and compounds. This study has focussed on some of these aspects, comparing a novel topical steroid (fluticasone) and a dry powder inhaler device loaded with budesonide (Turbuhaler™) with placebo.

In the present study we used a symptom score technique. This is a well-established method both in challenge experiments and in natural allergic rhinitis (Pipkorn et al., 1987). It would have been desirable also to use an objective method of monitoring the effect of the different treatments. Due to the multi-centre trial fashion of the present study, however, this was not possible to perform for practical reasons. In order to strengthen the results an open questioning of the treatment efficacy at the end of the study was also made. It would have been desirable in order to reveal any possible differences between the study medications that more patients were included into the study. However, for practical reasons this was not possible. It could also be speculated that if the patients had more pronounced symptoms we could have been able to disclose differences between the various treatments. To disclose any true differences in efficacy between the active treatments each patient

should have been exposed to the same daily amount of allergen. However, when studying natural allergic rhinitis this is not possible. At least the different kinds of perennial allergies should be equally distributed in the different treatment categories. This seems however to be achieved, as seen in Table 2.

Although the symptoms were mild and the number of patients was relatively small, we could demonstrate a significant reduction of the nasal symptoms for all active treatments as compared to placebo. The relatively milder lower symptoms score observed in this study is not so unexpected, because patients with perennial allergic rhinitis do not have the same extreme exposure to allergen as patients with seasonal allergic rhinitis have; they have a rather more continuous low-grade exposure. There are indications that the average scores for runny nose and sneezing were lower in this study than in earlier studies with a similar approach (Bunnag et al., 1992). Also, in this study the baseline score for sneezing was significantly lower for budesonide (400 μg) than for the other treatment groups. Since the study was only partly blinded, there was a risk for bias of the investigators and their possible preference for one or the other of the two studied glucocorticosteroids. The ideal design of the study would have been a placebo control with respect to fluticasone as well. Unfortunately, this could not be realized because of practical pharmaceutical reasons. In the compliance measurements there was a borderline significant difference (p=0.058) between fluticasone and the 400-μg budesonide groups. However, it should be observed that this comparison between treatments partly suffers from different dosage methods.

In conclusion, similar to previous studies we could demonstrate that budesonide delivered as pure powder (Pedersen et al., 1991; Andersson et al., 1993) and fluticasone (Scadding et al., 1991) all were effective and safe treatments for allergic rhinitis. We have also for the first time compared these novel treatments and no clinical differences between the active treatments have been disclosed.

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