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Two-dose beclomethasone dipropionate aerosol in the treatment of seasonal allergic rhinitis

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SUMMARY

Seventy patients with seasonal allergic rhinitis and with positive skin test to birch pollen were treated during the birch pollen season for three weeks in a randomized, double-blind placebo controlled, multicenter study. Nineteen patients were treated with beclomethasone dipropionate aerosol (50 µg/puff) one puff per nostril × 4 (daily dose 400 µg), 20 patients with beclomethasone dipropionate aerosol two puffs per nostril × 2 (daily dose 400 µg), 15 patients with placebo one puff per nostril × 4, and 16 patients with placebo two puffs per nostril × 2. Efficacy of the therapy was assessed through rhinoscopy (swelling and secretion of the mucous membrane) and measuring the nasal peak expiratory flow (NPEF) before, during and at the end of the trial. Nasal symptoms and the use of antihistamine tablets were recorded for five days before the trial and daily throughout the trial. Atmospheric pollen concentrations were recorded daily and the treatment was started two days after the air pollen counts had exceeded 10/m^3. The severity of the nasal symptoms was compared in the statistical analysis before the trial, during the pollen season without treatment and at the time of peak pollen counts during the treatment. Both active regimens controlled the symptoms effectively ($p < 0.01$) and both placebos showed no significant effect on the symptoms. In rhinoscopy, both active drugs reduced the swelling of the mucous membrane and the difference was significant ($p < 0.05$). No statistical differences were found in the NPEF or in the use of antihistamine tablets between the four groups. In conclusion this study showed that two-dose beclomethasone dipropionate with a daily dose of 400 µg is effective in the treatment of seasonal allergic rhinitis.

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INTRODUCTION

Beclomethasone dipropionate intranasal aerosol at a daily dose of 400 µg is widely used for the treatment of seasonal and perennial allergic rhinitis. The recommended administration is one puff of 50 µg from a pressurized cannister into each nostril four times daily. There is no controlled study comparing other frequencies of administration in the treatment of seasonal allergic rhinitis. In Munch et al.'s (1981) open study no differences were found in the efficacy of beclomethasone dipropionate when administered 100 µg four times or 200 µg twice daily in the treatment of hay fever due to grass pollen. We have compared a two-dose and a four-dose administration of intranasal beclomethasone dipropionate at a daily dose of 400 µg in allergic rhinitis due to birch pollen in a placebo controlled randomized multicenter study.

MATERIAL AND METHODS

Patients

Seventy-six adult patients (47 females and 29 males) who gave their informed consent entered the study. The age of the patients ranged from 16 to 57 years with a mean age of 27.5 years. There were no statistically significant differences in the age, sex, height and weight between the treatment groups. All patients had had nasal symptoms requiring drug therapy at least for two pollen seasons but none of them had received immunotherapy during the last two years. All had a positive skin test to birch pollen. Patients with bronchial asthma, nasal polyposis, atrophic rhinitis, and chronic sinusitis were excluded, as well as pregnant women or women without effective contraception. All the accepted 76 patients were asked to stay in the same locality for the treatment period. Patients did not use nasal drops, systemic steroids or disodium cromoglycate either in the nose or in the eyes.

Design of the study

All the patients were examined before the pollen season (day 0, Figures 2, 3). The rhinoscopic findings and the peak nasal expiratory flow (NPEF) were recorded. NPEF was measured with a Wright peak flow meter five times. The first two exhalations were excluded, and the mean of the last three was the final NPEF. The basic symptoms were recorded for five days before the pollen season (days 1–5, Figure 1). Sneezing, nasal discharge, nasal blockage, nasal itching, redness and itching of the eyes were recorded using a scale from 0 to 3 (0 = no symptoms; 1 = light symptoms; 2 = moderate symptoms; 3 = severe symptoms). The patients evaluated also their general condition daily, grading it ordinary, better, much better, worse, or much worse than ordinary.

The drugs used were beclomethasone dipropionate aerosol, containing 50 µg of active drug in each puff, and its placebo aerosol. The patients were randomly divided into four groups with daily doses of active drug 50 µg per nostril four

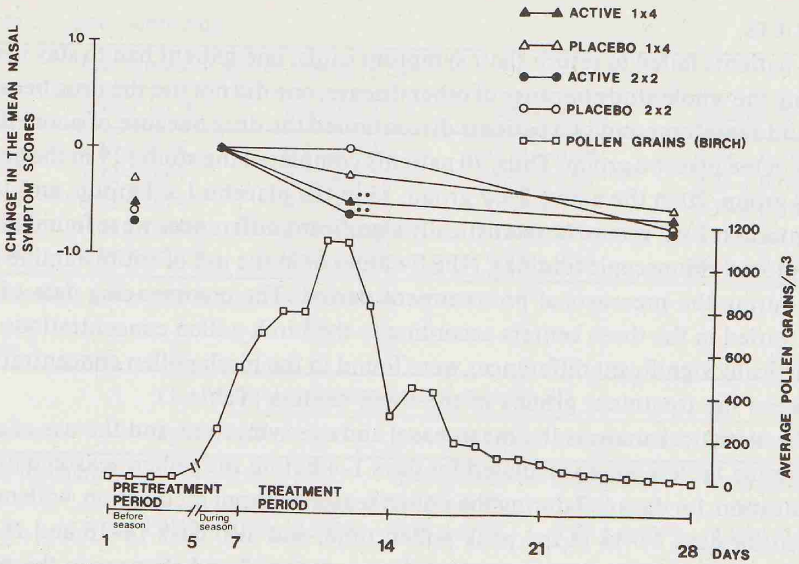

Figure 1. Change in the mean daily nasal symptom scores (sneezing, nasal discharge, itching and blockage) for each of the four treatment groups and corresponding average birch pollen concentration.

times (19 patients), placebo aerosol one puff per nostril four times (18 patients), active drug two puffs per nostril twice (19 patients) and placebo aerosol two puffs per nostril twice (20 patients). The patients were instructed in the correct use of the nasal aerosol at the first visit and illustrated instructions were included in every package. The patients were allowed to use antihistamine tablets (Phenylephrin. tannas 25 mg, Chlorphenamin. tannas 6 mg, Mepyramin. tannas 37.5 mg). The use of the tablets was recorded daily by the patient and the tablets were counted at the end of the trial by the doctor.

The patients were informed, when the birch pollen concentration reached the amount of 10 grains/m^3 and the symptoms were then recorded for two days without medication (days 6–7, Figure 1), after which the treatment with intranasal aerosol was started and the symptoms were daily recorded on the symptom cards (days 8–28). In the middle and at the end of the study (days 17 and 28) the patients were examined by the same doctor as before the pollen season. Nasal secretion and nasal mucosal swelling were evaluated using a scale from 0 to 2 (0 = nil, 1 = slight, 2 = severe) and NPEF was measured.

Birch pollen concentrations were recorded daily in all the centers where this study was performed (Turku, Kuopio, Oulu) using a Hirst Burkhard Trap. In the statistical analysis the paired Student's t-test was used in the comparison between the groups. Friedman two way analysis of variance and Student's paired t-test were used in the comparisons within the groups.

RESULTS

Two patients failed to return their symptom cards, one patient had to stay inside during the whole study because of other disease, one did not use the drug because of mild symptoms and two patients discontinued the drug because of poor effect, both in the placebo group. Thus, 70 patients completed the study; 19 in the active 1 × 4 group, 20 in the active 2 × 2 group, 15 in the placebo 1 × 4 group, and 16 in the placebo 2 × 2 group. No statistically significant differences were found in the symptoms, rhinoscopic findings, NPEF-values or in the use of antihistamine tablets during the preseasonal pretreatment period. The commencing date of the trial varied in the three centers according to the birch pollen concentrations. No statistically significant differences were found in the birch pollen concentrations between the treatment groups in the three centers (Table 1).

In the statistical analysis the mean nasal and eye symptoms and the use of antihistamine tablets were calculated for days 1–4 before the pollen season without medication, for days 6–7 during the pollen season without medication, with medication for days 11–13 at the peak pollen time, and also days 14–16 and 26–28. Maximum nasal symptoms appeared during days 6–7 and changes in the mean nasal symptom scores are shown in Figure 1. Both active drugs reduced the mean nasal symptoms (nasal discharge, blockage, itching and sneezing) significantly ($p < 0.01$) between days 6–7 and 11–13. The mean scores for each nasal symptom are shown in the Table 3. There was no statistically significant improvement in any of the symptoms in the placebo 2 × 2 group. In the placebo 1 × 4 group only nasal blockage was decreased ($p < 0.05$) between days 6–7 and 11–13. In comparison between the groups the mean nasal symptoms improved significantly ($p < 0.01$) in the active 2 × 2 group compared with its placebo.

The active 1 × 4 drug reduced the eye symptoms significantly ($p < 0.01$) whereas no significant differences were seen in the 2 × 2 group or in the placebo groups. However, in the 1 × 4 group eye symptom scores during days 6–7 were significantly higher than in the other groups (Table 2). In both active groups the patients' general condition, evaluated daily on the symptom card, was significantly improved ($p < 0.01$) between the days 6–7, 11–13 and 14–16. Compared with placebo the difference was significant ($p < 0.01$) in the 2 × 2 group. No significant dif-

Table 1. Average pollen grains/m^3 during the study.

	average pollen grains ± SD/m^3			
day	active 1 × 4	placebo 1 × 4	active 2 × 2	placebo 2 × 2
1– 4	0.16 ± 0.43	0.10 ± 0.35	0.16 ± 0.43	0.23 ± 0.51
6– 7	470 ± 502	522 ± 478	472 ± 471	364 ± 486
11–13	993 ± 443	1023 ± 573	1018 ± 553	1024 ± 494
14–16	415 ± 219	387 ± 225	384 ± 193	405 ± 215
26–28	16 ± 4	18 ± 16	17 ± 14	15 ± 7

Table 2. Eye symptoms.

	eye symptom scores, mean ± SD			
day	active 1 × 4	placebo 1 × 4	active 2 × 2	placebo 2 × 2
1- 4	0.13 ± 0.38	0.25 ± 0.40	0.13 ± 0.38	0.13 ± 0.29
6- 7	1.22 ± 0.97	0.75 ± 0.72	0.58 ± 0.61	0.63 ± 0.68
11-13	0.61 ± 0.74**	0.75 ± 0.62	0.65 ± 0.81	0.79 ± 0.58
14-16	0.61 ± 0.64**	0.75 ± 0.93	0.53 ± 0.63	0.65 ± 0.70
26-28	0.14 ± 0.30**	0.42 ± 0.88	0.35 ± 0.56	0.13 ± 0.22

** $p < 0.01$, compared with the 6-7th days' values.

Table 3.

		nasal symptom scores, mean ± SD			
symptom	day	active 1 × 4	placebo 1 × 4	active 2 × 2	placebo 2 × 2
nasal discharge	1- 4	0.66 ± 0.62	0.48 ± 0.65	0.69 ± 0.85	0.50 ± 0.50
	6- 7	1.28 ± 0.86	0.88 ± 0.83	1.47 ± 0.70	1.00 ± 0.52
	11-13	0.77 ± 0.58**	0.78 ± 0.57	0.92 ± 0.72**	1.06 ± 0.73
blockage	1- 4	0.38 ± 0.49	0.67 ± 0.74	0.75 ± 0.75	0.54 ± 0.60
	6- 7	1.19 ± 1.00	1.21 ± 0.66	1.20 ± 0.82	0.96 ± 0.72
	11-13	0.60 ± 0.66**	0.71 ± 0.49*	0.50 ± 0.59**	0.77 ± 0.71
itching	1- 4	0.36 ± 0.52	0.29 ± 0.41	0.46 ± 0.52	0.15 ± 0.29
	6- 7	0.81 ± 0.99	0.54 ± 0.54	1.15 ± 0.84	0.58 ± 0.67
	11-13	0.42 ± 0.52	0.33 ± 0.43	0.57 ± 0.60**	0.63 ± 0.71
sneezing	1- 4	0.29 ± 0.46	0.52 ± 0.48	0.63 ± 0.48	0.48 ± 0.47
	6- 7	1.11 ± 0.93	0.93 ± 0.78	1.13 ± 0.92	0.88 ± 0.77
	11-13	0.44 ± 0.48**	0.78 ± 0.65	0.68 ± 0.56*	0.85 ± 0.56

* $p < 0.05$, ** $p < 0.01$, compared with the 6-7th days' values.

ferences were seen in the use of antihistamine tablets between the four groups. Nasal mucosal swelling, evaluated in rhinoscopy, increased more in placebo groups ($p < 0.05$), whereas no significant increase in mucosal swelling was seen in active groups during the pollen season (Figure 2). There were no statistically significant differences between the treatment groups in nasal secretion evaluated in rhinoscopy (Figure 3). No significant changes were seen in NPEF-values between the groups.

DISCUSSION

During the last few years there has been a tendency towards fewer administrations in the treatment of allergic rhinitis. There have been many attempts to synthetize new nasal steroids, not necessarily more potent than beclomethasone dipropionate, but effective with fewer daily administrations. The efficacy of intranasal beclomethasone dipropionate in seasonal and perennial allergic rhinitis at 400 µg daily in four doses is well documented. Holopainen, Malmberg and Binder (1979) showed in the follow-up study of patients with perennial allergic rhinitis

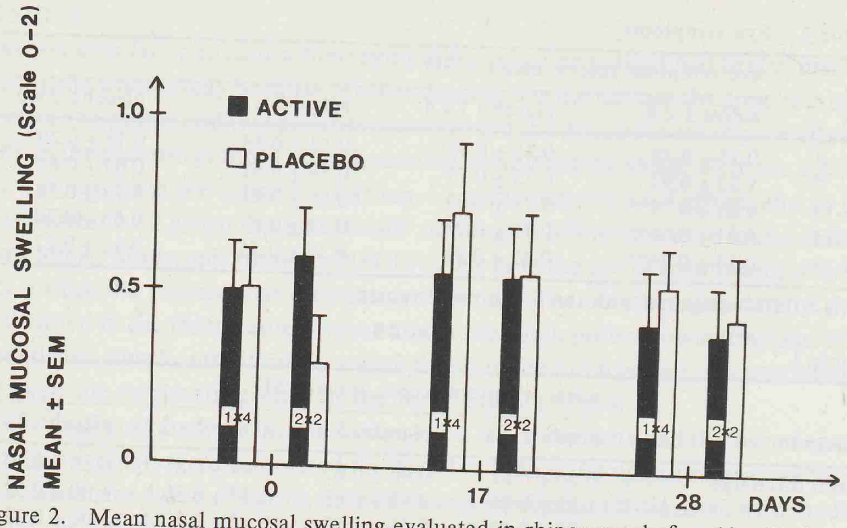

Figure 2. Mean nasal mucosal swelling evaluated in rhinoscopy before (day 0), during (day 17) and at the end of the trial (day 28).

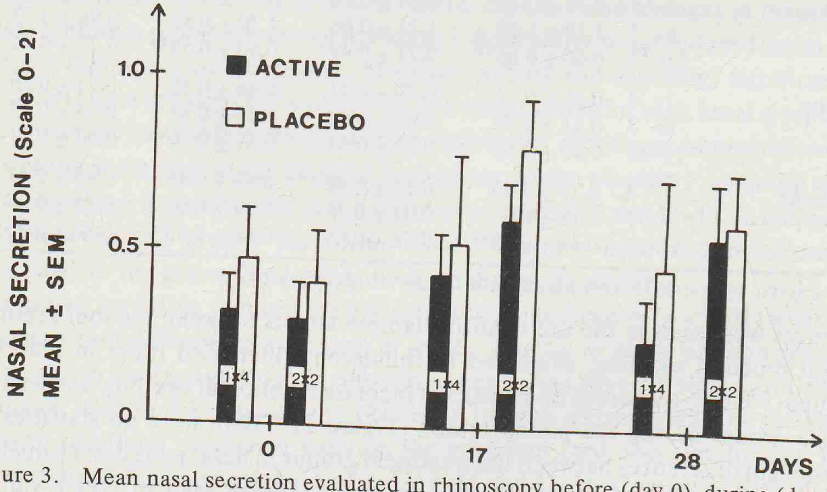

Figure 3. Mean nasal secretion evaluated in rhinoscopy before (day 0), during (day 17) and at the end of the trial (day 28).

that the daily dose can be reduced, in which case the side-effects, such as irritation and drying of the nasal mucosa, are diminished. Thus, the harmfull effect of the drug on the nasal physiology is minimized and the treatment is more convenient for the patient.

Our multicenter study was standardized in all centers by the daily pollen counts and the four treatment groups were identical in that point. It was possible that some patients had symptoms of perennial allergic rhinitis during the pretreatment preseasonal period. However, during that period no statistically significant

differences in the nasal symptom scores were found between the groups. To eliminate interpersonal variation in the nasal symptoms, we noted – in addition to the mean symptom scores – the change in the daily symptoms, too, and so the mean symptom change scores were also calculated (Figure 1).

We are of the opinion that this calculation should be done, at least in all non-crossover studies.

This study revealed that rhinoscopy is useful in the evaluation of the drug effect. The degree of the mucosal swelling is a better indicator than nasal secretion seen in rhinoscopy. In this study the rhinoscopy was performed in each patient always by the same doctor. The differences might have been greater, if the second examination had been made during the peak pollen time. Nasal peak expiratory flow measurements showed no statistically significant differences between the treatment groups. This might be due to the clearing effect of the placebo aerosol, since in the placebo 1×4 group the nasal blockage was improved ($p < 0.05$) but no differences were found in the other nasal symptoms or in the placebo 2×2 group. Also Hillas et al. (1980) found out in a study of patients with perennial allergic rhinitis that beclomethasone dipropionate placebo aerosol was better than sodium cromoglycate powder placebo and there was no difference in patients' final drug preference between sodium cromoglycate, sodium cromoglycate placebo of beclomethasone dipropionate placebo. We agree with Hillas et al. (1980) that the symptomatic improvement with placebo can not be attributed only to "placebo effect" but possibly also to the benefits of regular nasal douching.

According to this study seasonal allergic rhinitis can be treated effectively with 400 µg of beclomethasone dipropionate aerosol divided in two doses; two puffs per nostril twice daily. The drug is better distributed when one puff is taken on the upper part of the nose and another on the lower part of the nose than when using one puff administration. This was shown in a cadaver model by Mygind and Vesterhauge (1978). This distribution of the drug is best achieved with the adapter at right angle to the aerosol cannister (Mygind and Vesterhauge, 1978) and the applicator used in this study fulfilled this criteria. This mode of therapy is convenient for the patient and, due to the fewer administrations, is unlikely to cause any harm on the normal nasal physiology.

ZUSAMMENFASSUNG

70 Patienten mit allergischer Rhinitis und positiven Hautreaktionen gegenüber Birkenpollen wurden z.Z. der Birkenblüte während drei Wochen in einer randomisierten, multizentrischen Doppelblinduntersuchung behandelt. 19 Patienten erhielten Beclomethason-Dipropionat-Aerosol. 4mal täglich ein Spraystoss (Wirkstoffgehalt 50 µg) pro Nasenöffnung (Gesamttagesdosis 400 µg), 20 Patienten Beclomethason-Dipropionat-Aerosol, 2mal täglich zwei Spraystösse pro Na-

senöffnung, 15 Patienten Placebo, 4mal täglich ein Spraystoss pro Nasenöffnung, und 16 Patienten Placebo, 2mal täglich 2 Spraystösse pro Nasenöffnung. Die Wirksamkeit der Behandlung wurde rhinoskopisch (Schwellung und Sekretion der Schleimhaut) und durch Messung der maximalen Ausatemstromstärke (NPEF) vor und während sowie zum Schluss der Untersuchung beurteilt. Nasensymptome und der Verbrauch von Antihistamin-tabletten wurden während fünf Tage vor, und täglich während der Untersuchung registriert. Die Pollenkonzentrationen in der Luft wurden täglich registriert, und die Behandlung wurde zwei Tage nach Überschreiten des Grenzwertes von 10/m^3 eingeleitet. Der Schweregrad der Nasensymptome wurde vor der Prüfung, während der therapiefrieen Pollenperiode und zum Zeitpunkt der höchsten Pollenkonzentrationen während der Behandlung in der statistischen Analyse beurteilt. Beide aktiven Behandlungsregimes konnten die Symptome wirksam kontrollieren ($p < 0.01$), während beide Placeboregimes keine signifikante Wirkung auf die Symptome ausübten. Rhinoskopisch konnten beide aktiven Dosisregimes die Schwellung der Schleimhaut reduzieren, und der Unterschied zum Placebo war signifikant ($p < 0{,}05$). In Bezug auf die maximale Ausatemstromstärke oder auf die Einnahme von Antihistamintabletten fanden sich zwischen den Gruppen keine statistischen Unterschiede. Es liess sich also zeigen, dass die Zwei-Dosis-Beclomethason-Dipropionat-Behandlung mit einer Tagesdosis von 400 µg eine polleninduzierte allergische Rhinitis wirksam bekämpft.

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