

Intramuscular betamethasone dipropionate vs. topical beclomethasone dipropionate and placebo in hay fever

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A double-blind, double-dummy comparative study was made of 30 adult birch pollen-allergic outpatients with seasonal rhinoconjunctivitis. They were treated with either topically applied beclomethasone dipropionate 100 µg in each nostril twice daily for 4 weeks, placebo, or an injection of 2 ml of a suspension containing 5 mg betamethasone dipropionate and 2 mg betamethasone disodium phosphate per ml (Diprosan®) immediately prior to the birch pollen season. Placebo- and topical steroid-treated patients experienced an increase in rhinoconjunctivitis symptoms, i.e. nasal blockage, nasal itching, rhinorrhea, sneezing and eye symptoms, and placebo-treated patients used significantly more antihistamine tablets during the pollen season. Diprosan-treated patients experienced fewer symptoms on all measured parameters. We concluded that one injection of Diprosan immediately prior to the birch pollen season produces significantly fewer rhinoconjunctivitis symptoms than does placebo and topical steroid treatment.

Key words: allergic rhinitis; corticosteroid; hay fever; depot steroids.

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Hay fever is a common disease in general practice (7), and in Denmark about 12 % of patients are treated with an intramuscular injection of depot steroid prior to or early in the pollen season, whereas only 6 % of patients are treated with topically applied steroids (3). We and others have shown that the suppressive effects on the hypothalamic pituitary adrenal axis measured by ACTH test (10) are restored after approximately 3 weeks with one injection of 2 ml Diprosan® (2, 4).

In this study we have compared the effect of betamethasone dipropionate and betamethasone disodium phosphate intramuscularly with topically applied beclomethasone dipropionate and placebo, a comparison which we believe has not been previously made (6).

MATERIAL AND METHODS

In this double-blind double-dummy comparative study 31 birch pollen-allergic patients were

randomly treated with either an injection of 2 ml of a suspension containing 5 mg betamethasone dipropionate and 2 mg betamethasone disodium phosphate per ml (Diprosan), or topically applied beclomethasone dipropionate (Aldecin®) 2 puffs (50 µg/puff) in each nostril twice daily for 4 weeks, or placebo (Fig. 1). Outpatients fulfilling the following criteria (8) were included:

- more than 15 years of age
- a positive past anamnesis of allergic rhinoconjunctivitis during previous birch pollen seasons (April and May)
- a positive skin prick test to birch pollen (Allergologisk Laboratorium, Copenhagen) (at least the same size as that of the histamine test (1 mg/ml) and/or a positive class 2 RAST or higher).

Patients undergoing continuous hyposensitisation were not included, neither were patients treated with steroids during the 3 months prior

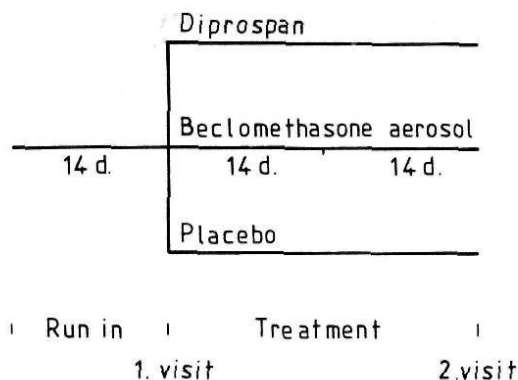


Fig. 1. Study design.

to the birch pollen season. Patients with diabetes, arterial hypertension, diseases of the liver or thyroid gland, and pregnant, were not included. All patients gave their informed consent to participation and the local Ethics Committee approved the study design. One patient left the study after treatment with intramuscular betamethasone for personal reasons. Results are based on a material of 30 patients (13 women and 17 men) with a mean age of 32 years (range 17–52 years). Ten patients were treated with intramuscular betamethasone, 9 patients with topically applied beclomethasone, and 11 patients took placebo.

Medication

Coded ampoules of Diprosan (betamethasone dipropionate and betamethasone disodium phosphate) and placebo, and coded pressurized aerosols were used. (Aldecin and placebo ampoules were provided by Essex Pharma A/S, Copenhagen.) The study was patient and observer blinded and Diprosan 2 ml was injected intramuscularly immediately before the birch pollen season on either the 28th, 29th or 30th of April and in 8 patients a few days later. Concomitantly, patients on active Diprosan were treated with placebo nasal aerosols twice daily for the following 4 weeks. The randomisation code remained unbroken until the study was terminated. Patients were

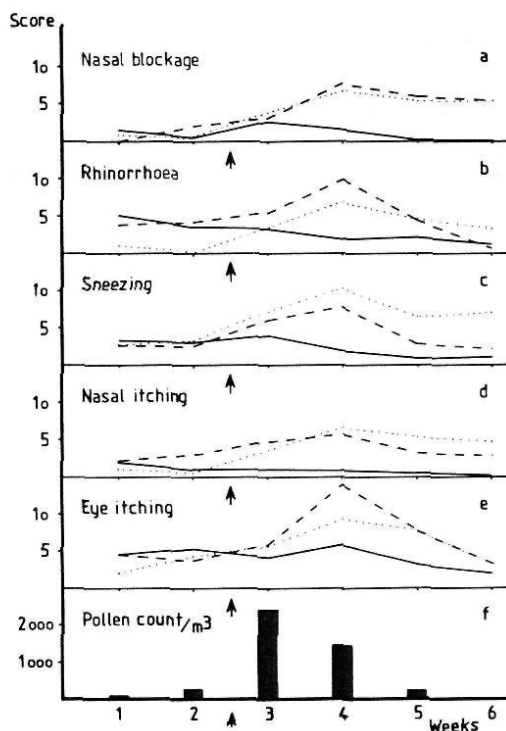


Fig. 2. a-e) Mean weekly symptoms scores. f) mean weekly score for pollen counts. Arrows denote when therapy was initiated. Solid lines: patients treated with 2 ml betamethasone dipropionate and betamethasone disodium phosphate i.m. ($n = 10$). Broken lines: patients treated with 400 μ g beclomethasone dipropionate daily ($n = 9$). Dotted lines: patients on placebo ($n = 11$).

allowed to use an antihistamine – azatadine (Verbén®) 1–2 mg/24 h if necessary.

Diprosan 2 ml contains 10 mg betamethasone dipropionate (slow release) and 4 mg betamethasone disodium phosphate (fast release). Betamethasone disodium phosphate is rapidly absorbed, producing peak blood levels in about 60 min, immediately hydrolysed and almost completely excreted after 48 h, whereas betamethasone dipropionate is more slowly metabolized and excreted over a prolonged period. More than 50 % of betamethasone dipropionate is excreted within 10 days according to the manufacturer (4).

Beclomethasone dipropionate 200 μ g were applied topically by the patients twice daily for 4 weeks.

Symptoms recording

During a 14-day run-in period - to examine baseline values - and 4 weeks after treatment was initiated, patients recorded the degree of the following symptoms using a 5-graded scale (0-4): nasal blockage, nasal itching, sneezing, rhinorrhea, and eye symptoms. They also recorded their daily intake of antihistamine tablets. After the trial all medication was controlled and nasal aerosol weighed in order to control medication consumption.

Pollen counts

Pollen was collected in a Burkard trap, placed 15 m above ground level in the city of Copenhagen. A mean of the daily pollen counts for 1-week periods was calculated on the basis of the data published by the

Aerobiological Group, Danish Asthma & Allergy Association.

Statistical analysis

The differences between means of the total symptoms score and antihistamine consumption during a 2-week period were tested using Student's *t*-test for unpaired samples. Means were calculated as mean score per week. $P < 0.05$ was significant.

RESULTS

All patients used the amount prescribed except two patients on placebo, two on beclomethasone dipropionate and five on betamethasone dipropionate/betamethasone disodium phosphate, who had only used their nasal aerosol sporadically because of lack of symptoms.

Means of scores calculated per week are shown in Fig. 2a-e. Fig. 2f shows total pollen count calculated on a weekly basis.

Placebo-treated patients experienced a rise in all symptoms, particularly nasal blockage, nasal secretion, sneezing and eye symptoms, and used significantly more antihistamine tablets during the pollen season than with the two other treatments ($P < 0.01$) Table 1). Aldecin treatment seemed to have most effect on sneezing and least effect on eye symptoms. Patients in this group used significantly fewer Verben

Table 1

Mean daily use of antihistamine tablets in entire period following injection of 2 ml betamethasone dipropionate/betamethasone disodium phosphate, beclomethasone dipropionate topically applied, and placebo

Treatment	Mean no. of antihistamine tablets/day	
Depot steroid	0.04	] $P < 0.01$]
Topically applied steroid	0.08	
Placebo	0.46	

Table 2

Total daily symptom score calculated as means $\pm$ SEM on a weekly basis. P values are calculated for differences between full treatment periods of 4 weeks

Treatment	Injected BD/BDP	Inhaled BD	Placebo	
Week No.				
1	3.2 (0.7)	2.6 (0.8)	1.7 (0.3)	] Run-in period]
2	2.6 (0.9)	3.1 (0.4)	2.0 (0.8)	
3	2.9 (0.6)	5.1 (0.5)	4.8 (0.7)	
4	2.4 (0.8)	9.1 (1.3)	8.0 (0.7)	
5	1.4 (0.6)	5.0 (0.9)	6.3 (0.6)	
6	0.9 (0.3)	3.0 (0.8)	4.7 (0.7)	
	] $P < 0.01$]			
	] $P < 0.01$]			

BD: betamethasone dipropionate; BDP: betamethasone disodium phosphate.

tablets during the 4-week treatment compared to placebo ($P < 0.01$) (Table 1).

Intramuscular betamethasone dipropionate/betamethasone disodium phosphate protected the patients against rhinoconjunctivitis symptoms throughout the entire observation period, being primarily effective against nasal blockage, nose itching and sneezing. When comparing the sum of the daily rhinoconjunctivitis symptoms for the entire treatment period of 4 weeks, intramuscular betamethasone dipropionate/betamethasone disodium phosphate proved to be superior to both topically applied steroid and placebo ($P < 0.01$) (Table 2).

Side effects

Two patients treated with betamethasone dipropionate/betamethasone disodium phosphate complained of an itching rash during the first 3–4 days. No severe side effects were seen.

DISCUSSION

It has been discussed for years whether injected depot steroids produce systemic side effects. By means of the ACTH test we have shown that the HPA axis is less suppressed with 10 mg betamethasone dipropionate and 4 mg betamethasone disodium phosphate i.m. than with oral prednisolone 7.5 mg/day (2). Further, suppression cannot be detected 3 weeks after one injection with betamethasone dipropionate, indicating that the adrenal function has normalized (2).

d'Souza et al. (7) found, as we did (2) that the best parameter for evaluating hay fever treatments is daily symptom recording.

It is somewhat surprising that the symptom score after topically applied beclomethasone dipropionate is similar to the scores after placebo, although sneezing and the use of additional antihistamine tablets was significantly reduced with the former. Topically applied steroids are known to be particularly effective against nasal blockage (4). One explanation for these findings might be that our patients were treated with topically applied steroids simultaneously with the increase in pollen and not 1 or 2 weeks

before, which may have delayed the clinical efficacy of beclomethasone dipropionate in our study (4).

Another possible reason for the difference in efficacy of the two active treatments is the difference in steroid potency. Very little is known about the equipotency of the various steroids and administration routes. However, we used the recommended doses of the two drugs on the indication allergic rhinoconjunctivitis.

It seems likely that intramuscular injection of betamethasone dipropionate/betamethasone disodium phosphate has advantages over topically applied steroid and placebo in the treatment of birch pollinosis. Furthermore, it is easily administered and, so far, no severe side effects have been reported provided contraindications are respected (i.e. children, pregnant woman, peptic ulcer disease, active tuberculosis, herpes, hypertension, diabetes or immunosuppressed patients) (1).

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