

Powder administration of pure budesonide for the treatment of seasonal allergic rhinitis

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The objective of this study was to compare the efficacy and safety of a pure powder formulation of budesonide, delivered from a new multi-dose dispenser for nasal drug application, with the commercially available budesonide pressurized aerosol, and with placebo. Of 116 patients with grass pollen-induced allergic rhinitis, 112 finished the study, which comprised a 4-week treatment period, preceded by a 1-week run-in period. The patients were randomized to four parallel treatment groups: budesonide powder 400 µg daily; budesonide powder 800 µg daily; budesonide aerosol 400 µg daily; and placebo powder. Treatment was given once daily in the morning. The study was double-blind regarding comparison between budesonide powder and placebo. Assessment of efficacy, made by comparing mean scores of nasal symptoms and use of rescue medication, showed equal efficacy of all three budesonide groups compared with placebo. There were no differences between budesonide- and placebo-treated groups with regard to side effects. Budesonide treatment had no demonstrable effect on the HPA-axis assessed by measurement of 24-h urine cortisol. We conclude that budesonide, delivered as pure powder from a multi-dose dispenser, is effective and safe for the treatment of seasonal allergic rhinitis. This new formulation is a good alternative to the commercially available preparations, as it does not contain carrier gas, preservatives or lubricants.

Key words: allergic rhinitis; glucocorticoid; steroid; budesonide; powder formulation; multi-dose dispenser.

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Nasal inhalation of the topically active glucocorticoid, budesonide, for the treatment of rhinitis has been available for a number of years and has shown to be effective and safe (2, 3). Budesonide is commercially available in the form of a freon-propelled pressurized aerosol (Rhinocort[®]) and as a water-based suspension delivered from a metered-dose pump spray (Rhinocort Aqua[®]).

A new device has been developed for powder administration of budesonide for topical treatment of rhinitis. This is a breath-actuated multi-dose inhalation device which is loaded with pure budesonide, and thus is free from additives such

as propellants, lubricants, preservatives, and carrier powder. This device makes drug release possible even at low nasal inspiratory flow rates.

PATIENTS AND METHODS

The trial was of a placebo-controlled, double-blind, randomized, parallel group design. The efficacy of budesonide given as a dry powder in two doses (400 µg/day and 800 µg/day) or as a freon-propelled pressurized aerosol (400 µg/day) and placebo (powder) was compared in symptomatic patients with grass pollen-induced allergic rhinitis. The comparison between budeso-



Fig. 1. The multi-dose dispenser used for nasal application of a pure powder formulation of budesonide.

nide powder and placebo was made double-blind and between powder and aerosol single-blind (investigator). The patients entered the study 1 week before the start of treatment in order to record their symptoms during a 7-day baseline period. Treatment with budesonide or placebo started after the run-in period and continued for 4 weeks.

The study was undertaken in Aarhus, Denmark, during the period 30.5–3.7.1989. The grass pollen season was defined by daily pollen counts from a Burkard trap, placed 15 m above ground level (The Aerobiological Group, The Danish Asthma-Allergy Society).

Patients were recruited by advertisement in a newspaper; 116 adults with rhinitis in the pollen season and a positive skin test to grass pollen (Phazet®, Pharmacia, Uppsala, Sweden) were

included and 112 completed the trial. Their mean age was 30.5 years (range 18–59); 41 were women and 71 men. All volunteers gave informed consent to participate, and the protocol was approved by the Ethics Committee of Aarhus. Patients with perennial rhinitis, severe nasal blockage, steroid-requiring asthma, and women who were or were likely to become pregnant, were not included. Twenty-seven of the patients also suffered from birch pollen allergy (season: April-May).

Budesonide dry powder for nasal inhalation, 200 µg/inhalation and 400 µg/inhalation, and powder placebo were supplied coded by Draco, Lund, Sweden, who also supplied budesonide pressurized aerosols, 100 µg/puff (Rhinocort®). The powder device was a multiple-dose inhaler (200 doses), similar to the device used for oral inhalation of budesonide (Pulmicort® Turbuhaler®), but with the mouthpiece exchanged with a nozzle (Fig. 1). All medication was given once daily in the morning. The pressurized aerosol was given as two puffs into each nostril (400 µg daily), and the powder as one inhalation in each nostril of 200 µg and 400 µg respectively (400 µg and 800 µg daily). The patients were instructed to close one nostril, place the inhaler in the other and take a short quick inhalation (sniff) (approx. 30 l/min).

The patients were allowed to take rescue medication as required: terfenadine tablets 60 mg (max. 2 daily) for nose symptoms, and antazoline-naphazoline eye drops for eye symptoms (1–2 drops p.r.n). Use of rescue medication was recorded daily.

Symptom evaluation was accomplished through the use of a diary. Every evening before retiring the patient evaluated symptoms over the preceding 24-h period. Symptoms evaluated were sneezing, runny nose, blocked nose, and eye itching. Scoring was made on a scale from 0 to 3 (0 = absent; 1 = slight; 2 = moderate; 3 = severe). After the treatment period the patients were also asked to evaluate the ability of the test medication to control nasal symptoms on a scale from 0 (symptoms aggravated) to 4 (complete control).

The patients measured nasal peak inspiratory flow (best of three) by a Youlton Peak In-

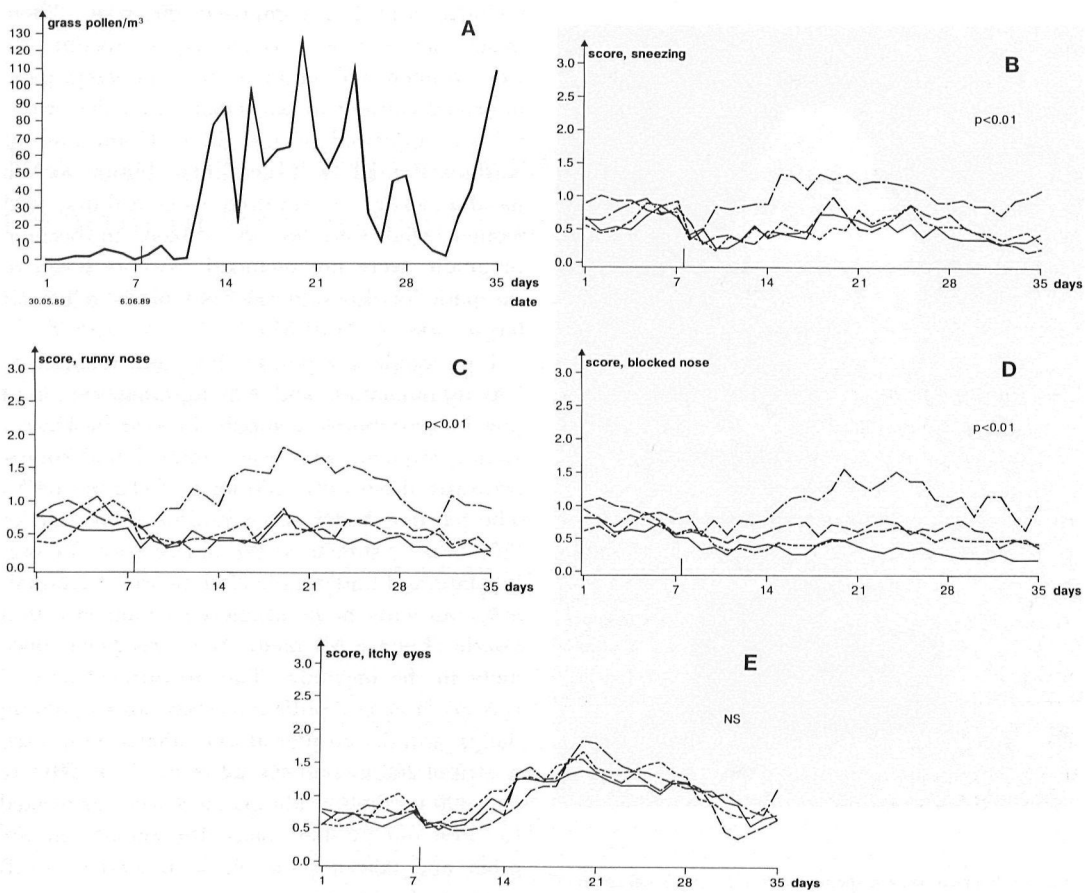


Fig. 2. Daily grass pollen count (A), nose symptom scores (B-D), and eye symptom scores (E) during baseline period and treatment period. Placebo = dotted/dashed line; budesonide aerosol = dotted line; budesonide powder 400 µg = dashed line; budesonide 800 µg = solid line.

spiratory Flow Meter after the run-in period and after the treatment period.

The patients were asked to record in the diaries any adverse experience, which included specific questions about nose dryness and nose

Table 1.

Weekly consumption of terfenadine tablets (number of tablets; mean ± SD)			
	Run-in period	Treatment period	Difference
Placebo	1.7 ± 3.0	5.3 ± 4.6	+ 3.6
Aerosol 400 µg	3.0 ± 3.4	1.8 ± 2.7	- 1.2
Powder 400 µg	3.9 ± 5.1	2.8 ± 3.8	- 1.1
Powder 800 µg	1.5 ± 2.9	1.1 ± 3.0	- 0.4

Table 2.

Weekly use of antazoline-naphazoline eye drops (number of drops; mean ± SD)			
	Run-in period	Treatment period	Difference
Placebo	4.9 ± 7.7	9.7 ± 9.5	+ 4.8
Aerosol 400 µg	8.1 ± 14.1	12.6 ± 15.3	+ 4.5
Powder 400 µg	7.6 ± 11.5	17.2 ± 18.4	+ 9.6
Powder 800 µg	7.0 ± 14.9	12.8 ± 12.7	+ 5.8

Table 3.

Patients' overall assessment of treatment efficacy
(score 0 = aggravated; score 1 = no control;
score 2 = minor control; score 3 = substantial control;
score 4 = total control) (number of patients)

Score	0	1	2	3	4
Placebo	4	12	4	3	3
Aerosol 400 µg	0	0	5	13	8
Powder 400 µg	0	1	3	12	12
Powder 800 µg	1	2	0	9	16

bleeding. During the treatment period they counted and recorded the number of sneezes over a 5-min period following test medication.

Influence on the HPA-axis was assessed by measuring 24-h urine cortisol. Urine was collected in the run-in period and on the last day of the treatment period.

Statistics

The mean values for the individual symptom scores over the 4-week treatment period were compared between the four treatments. The difference between run-in and treatment periods was compared within and between treatments. Wilcoxon's one- and two-sample tests were used in the analysis. The global assessment of treatment efficacy was analysed using Wilcoxon's rank sum test. Consumption of rescue medicine was compared between the treatment groups during the run-in and treatment periods. An unpaired t-test was used in the statistical analysis. Laboratory data were compared within each treatment group as well as between treatment groups. Statistical analysis was made with t-

tests. In all tests of significance two-tailed alternatives were used; $P < 0.05$ was considered as statistically significant.

RESULTS

In the run-in period there were no differences between the four treatment groups with regard to sneezing, runny nose, blocked nose or eye itching (Fig. 2B-D). In the treatment period, the placebo group had significantly more nasal symptoms than the three budesonide groups ($P < 0.01$ for sneezing, runny nose and blocked nose), which did not differ statistically significant from each other, although there was a tendency in favour of the powder 800 µg group with regard to nasal blockage in the last part of the treatment period (Fig. 2B-D).

There were no differences between the four treatment groups with regard to eye itching, during the run-in period and during the treatment period (Fig. 2E).

Regarding rescue medication, Table 1 shows the use of terfenadine tablets for nasal symptoms. There was a significant difference between the placebo group and the budesonide groups ($P < 0.01$), but not between the three budesonide groups. As seen in Table 2, there were no group differences in the use of eye drops.

An overall assessment of treatment efficacy showed a significant difference between the placebo group and the three budesonide groups ($P < 0.01$), but not between the three actively treated groups (Table 3).

The mean nasal peak inspiratory flow decreased from the run-in period to the treatment period in the placebo group, while it increased in all three budesonide groups ($P < 0.01$) (Table 4).

Table 4.

Results of nasal peak inspiratory flow before and after treatment (mean $\pm$ SD; l/min)

	Run-in period	Treatment period	Difference	P
Placebo	186 $\pm$ 63.2	155 $\pm$ 52.5	- 31	0.01
Aerosol 400 µg	162 $\pm$ 47.9	213 $\pm$ 63.8	+ 51	0.000
Powder 400 µg	179 $\pm$ 63.0	236 $\pm$ 70.8	+ 57	0.000
Powder 800 µg	181 $\pm$ 39.5	222 $\pm$ 53.0	+ 41	0.000

Table 5.

Nose dryness (number of patients with this symptom and, in parenthesis, number of days with the symptom in all patients)

	Run-in period (7 days)	Treatment period (28 days)
Placebo	8 (37)	12 (145)
Aerosol 400 µg	4 (16)	7 (88)
Powder 400 µg	6 (17)	6 (75)
Powder 800 µg	10 (63)	7 (84)

Patients answered daily on their diary card questions about the presence of such side effects as nose dryness and nose bleeding. As seen from Tables 5, 6 there was no difference between the placebo and the budesonide groups, between the three budesonide groups, or between run-in period and treatment period, when the different length of time (1 vs 4 weeks) was taken into account. The patients did not report other symptoms which were likely to be adverse effects from the medication. Nasal spraying and inhalation caused immediate sneezing on a few occasions. There was no difference between the groups (Table 7).

Table 8 shows that there was no significant difference between treatment groups with regard to change in mean 24-h urine cortisol levels before and after treatment.

DISCUSSION

For statistical reasons a large number of patients are needed in a drug-comparative study. We managed to include 116 patients with grass

Table 6.

Nose bleeding (number of patients with this symptom and, in parenthesis, number of days with the symptom in all patients)

	Run-in period (7 days)	Treatment period (28 days)
Placebo	3 (7)	8 (21)
Aerosol 400 µg	3 (6)	4 (6)
Powder 400 µg	0 (0)	5 (10)
Powder 800 µg	4 (8)	5 (21)

Table 7.

Sneezes induced by nasal medication (all days for all patients treated)

	Number of sneezes after medication (5 min)						
	0	1	2	3	4	5	6
Placebo	619	25	21	6	5	2	2
Aerosol 400 µg	609	20	28	15	12	4	0
Powder 400 µg	663	37	15	3	0	2	0
Powder 800 µg	712	16	8	5	1	2	1

pollen allergy and 112 completed the study. However, a large number of patients may be at the expense of patient selection. Some of the patients also had birch pollen allergy, as they had significant symptoms and needed rescue medication in the run-in period. However, it is unlikely that this has had any influence on group comparisons during the treatment period.

The study clearly showed that the new budesonide pure drug multi-dose dispenser is more effective than placebo. It also indicates that the powder formulation and the commercially available pressurized aerosol are equally effective, when administered in the same dosage. This comparison was not based on a double-blind double-dummy design, as we also wanted to test local side effects from the different types of spray devices. Theoretically, one would expect the powder formulation to be more effective than the pressurized aerosol, which gives an 80% drug deposition in the anterior non-ciliated part of the nose, while the powder to a greater extent reaches the middle and posterior parts (6). An earlier study comparing beclomethasone dipropionate as powder and as pressurized aerosol in nasal polyposis also showed

Table 8.

Urine cortisol levels at the end of the run-in period and at the end of the treatment period (mean ± SD; nmol/l)

	Run-in period	Treatment period	Difference
Placebo	70.2 ± 48.1	67.4 ± 34.0	- 2.8
Aerosol 400 µg	65.9 ± 36.1	73.8 ± 31.7	+ 7.9
Powder 400 µg	63.1 ± 32.5	71.8 ± 41.5	+ 8.7
Powder 800 µg	59.6 ± 35.2	59.6 ± 57.3	0.0

equal efficacy (6, 8). The same applies to comparisons between aqueous formulations and pressurized aerosols (4).

High-dose therapy with topical steroids has in recent years gained widespread use in the treatment of asthma. There is no reason to believe that a dose-response correlation should not exist also in rhinitis, but it has not been demonstrated. We find the pure budesonide formulation suitable for the study of high-dose therapy, but were unable to show any difference in efficacy between 400 µg and 800 µg a day. It is a possible explanation that the pollen counts were relatively low and the symptoms not severe. Patients with severe rhinitis may benefit from a higher dose, but this treatment cannot be recommended before controlled studies have shown it to be more effective than ordinary-dose treatment.

The local side effects: spray-induced sneezing, nose dryness and nose bleeding were carefully recorded in our study, and we were unable to show any difference between budesonide powder and pressurized aerosol, and between budesonide and placebo.

In principle, the new budesonide powder device has the advantage that it does not contain carrier gases, lubricants, or preservatives (1, 7). The multi-dose inhaler is as easy to use as the pressurized aerosol, and overspill to the nostril, occurring with aqueous pump sprays is avoided.

We conclude that budesonide pure powder multi-dose inhaler is effective and safe in the treatment of pollen rhinitis. It is a good alternative to the available spray types, and for theoretical reasons, it may even be preferable.

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