

Nasal inhalation of the glucocorticoid budesonide from a spacer for the treatment of patients with pollen rhinitis and asthma

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Glucocorticoid sprays are increasingly used for the treatment of allergic rhinitis and asthma. This therapy is highly effective, and side effects are few and mild. It was the aim of the present study to evaluate a physiological nasal inhalation technique, which results in airway deposition of the steroid molecule similar to that of inhaled allergen particles. Thirty adults with grass pollen-induced rhinitis and asthma inhaled the steroid molecule budesonide through the nose from a pressurized aerosol attached to a spacer device. Compared with inhalation of placebo, the treatment resulted in a significant reduction of nasal symptoms ($P = 0.005$), of bronchial symptoms ($P = 0.005$), but not of eye symptoms. In addition, nasal peak inspiratory flow ($P = 0.0003$) and oral peak expiratory flow ($P = 0.02$) increased. There was no difference between budesonide and placebo with regard to local side effects, such as nose bleeding, hoarseness, and irritation in mouth and throat. It is concluded that nasal inhalation of a steroid from a spacer offers effective therapy of pollen rhinitis and asthma without significant local side effects. This therapeutic modality may have advantages over the ordinarily used nasal and bronchial spray treatment in patients with both rhinitis and asthma, especially when conventional spray therapy is associated with local side effects.

Key words: allergic rhinitis; asthma; glucocorticoid; budesonide.

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The nose is an important integral part of the human airways, as a normal person at rest will exclusively breathe through the two nasal cavities. Particles in the inhaled air are largely deposited in the nasal airway, which acts as a filter, protecting the delicate gas-exchanging structures in the lungs (7). Some small particles, however, bypass the nasal filter and can reach the lower airways (1). When allergen particles are inhaled, their deposition can, in sensitized individuals, result in rhinitis and/or asthma.

Topical glucocorticoids are increasingly used for the treatment of rhinitis and asthma, allergic as well as non-allergic (2). In rhinitis, a relatively large amount of steroid is sprayed into the

nose by a pressurized aerosol or by a pump spray which both give an uneven distribution over the nasal mucosa (10, 11), and although local side effects are rare, they do occur (9, 13). In asthma, the steroid spray is inhaled through the mouth, which may result in the development of oral candidiasis (15). Although this side effect can now largely be avoided by use of a spacer device (14), oral inhalation is not logical for the treatment of a combination of rhinitis and asthma.

The aim of the present study was to test the hypothesis that a steroid drug, which is inhaled through the nose, can be effective both in rhinitis and in asthma. A deposition pattern which

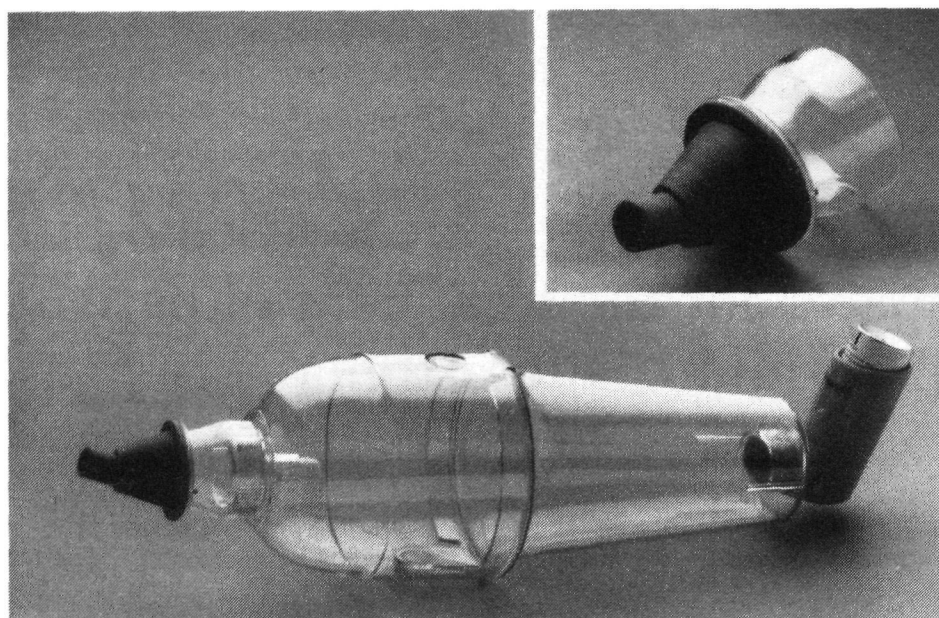


Fig. 1. Pressurized metered-dose aerosol, pear-shaped spacer device and nozzle used for nasal inhalation of budesonide.

is similar for drug and for allergen seems logical in order to get an optimum ratio between wanted anti-rhinitis/asthma effect and local adverse effects. We used an ordinary pressurized aerosol with budesonide delivered from a spacer device equipped with a nozzle. Moren & Newman (8) have recently shown that nasal inhalation from this device results in drug deposition both in nose and in bronchi.

PATIENTS AND METHODS

The design was a placebo-controlled, double-blind, cross-over study of patients with grass pollen-induced rhinitis and asthma. The grass pollen season in Denmark usually starts around June 1, and grass pollen counts fade during July. A 10-day run-in period was followed by two 14-day treatment periods. The run-in period started May 24, 1988 (± 1 day) and the treatment period June 3 (± 1 day). The patients

were allocated at random to placebo-budesonide or budesonide-placebo treatment.

The grass pollen season was defined by daily pollen counts from a Burkard trap, placed 15 m above ground level (Aerobiological Group, Danish Asthma-Allergy Association). The mean daily pollen counts for the two treatment periods were 37 and 28 respectively.

The study comprised 30 adults with a positive skin test/RAST to grass pollen, who had rhinitis in the pollen season and also asthma (cough, wheeziness or dyspnoea), during at least one of the last 5 seasons. Their mean age was 25.5 years (range 18–51); 16 were men and 14 women. All volunteers gave informed consent to participate, and the protocol was approved by the Ethics Committee of Aarhus. Patients with perennial rhinitis, asthma requiring steroid treatment, severe nasal blockage, and women who were, or were likely to become, pregnant, were excluded.

Table 1

Preference for treatment period (lowest mean score in 2nd week)

	Budesonide	None	Placebo	<i>P</i>
Nasal symptoms	21	3	6	0.005
Bronchial symptoms	18	8	4	0.005
Eye symptoms	11	4	15	0.74

Table 2

Preference for treatment period; specific nasal symptoms (lowest mean score in 2nd week)

	Budesonide	None	Placebo	<i>P</i>
Sneezing	18	5	7	0.013
Blocked nose	18	7	4	0.003
Runny nose	18	5	7	0.013

Test medication consisting of budesonide pressurized aerosols, delivering 100 µg per actuation, and identical placebo aerosols, were supplied coded by Draco, Lund Sweden. The patients took two inhalations through each nostril twice daily, i.e. a daily dosage of 800 µg budesonide. The aerosol was inhaled from a 0.75 l pear-shaped spacer device (Nebuhaler) equipped with a nozzle (Fig. 1). The patients were instructed to check nasal patency and only to inhale through a patent nostril. Following an exhalation they took a slow (2 s) maximal nasal inhalation through the device, with the other nostril closed, and held their breath for 10 s.

The patients were allowed to take rescue medication as required: terbutaline spray for asthma, Antistin-Privin eye drops for eye symptoms, oxymethazoline nose drops for nasal blockage, and terfenadine tables for nasal itching and rhinorrhea. Use of rescue medication was recorded daily.

The patients filled in a diary card every evening and graded eye, nasal and bronchial symptoms as 0 (absent), 1 (slight), 2 (moderate), or 3 (severe). In the morning and in the evening they measured nasal peak inspiratory flow (best of 3) with a Youlton Peak Nasal Inspiratory Flow Meter, and peak expiratory flow through the mouth (best of 3) by a Mini Wright Peak Flow Meter. At the end of the trial the record cards were used to give a preference

for one of the two treatment periods (lowest mean score in second week of period), with regard to eye, nasal and bronchial symptoms.

Every day the patients recorded on the diary card whether they had had any of a series of named side effects known to occur during topical steroid treatment (see Table 7). Side effects were scored 0 (absent), 1 (slight), 2 (moderate) or 3 (severe).

Wilcoxon's test was used for preferences and Student's paired t-test for the peak flow measurements.

RESULTS

The trial was completed by all 30 persons. Compliance was checked by weighing of canisters, which showed that the patients had followed the recommendation closely and taken an average of 7.8 puffs per day (prescribed number: 8 per day).

There was a highly significant preference for active treatment with regard to nasal symptoms (*P* = 0.005), bronchial symptoms (*P* = 0.005), but not eye symptoms (Table 1).

The results of specific nasal symptoms suggested a more pronounced effect on blockage than on sneezing and rhinorrhea (Table 2). With regard to bronchial symptoms there was a better effect on wheezing and breathlessness than on cough (Table 3), but few patients suffered from this symptom.

Table 3

Preference for treatment period; specific bronchial symptoms (lowest mean score in 2nd week)

	Budesonide	None	Placebo	<i>P</i>
Wheezing	16	10	4	0.006
Breathlessness	15	11	3	0.006
Cough	11	14	5	0.105

Table 4

Nasal peak inspiratory flow			
Mean + SD	Budesonide	Placebo	<i>P</i>
Morning	190 + 69	163 + 72	0.004
Evening	201 + 71	171 + 77	0.0003

There was a highly significant difference between budesonide and placebo periods with regard to nasal peak inspiratory flow ($P = 0.0003$) (Table 4). Measurement of oral peak expiratory flow showed a less marked difference between the two treatment periods ($P = 0.02$) (Table 5), but terbutaline spray was used more frequently during placebo than during budesonide treatment ($P = 0.03$) (Table 6). The use of rescue medication for nasal symptoms did not differ significantly between the two groups, although there was a clear trend (Table 6).

There was no difference between the two treatment periods with regard to any of the side effects mentioned on the diary card (Table 7).

DISCUSSION

The present study has confirmed our working hypothesis, i.e. nasal inhalation of the steroid molecule budesonide, given from an ordinary pressurized aerosol through a spacer device with a nozzle, is effective in controlling pollen-induced rhinitis and asthma symptoms. This provides good evidence that budesonide is deposited in the nasal and bronchial airways in a similar way as the 3 μm large particles used by Moren & Newman (8).

Due to the high linear velocity of a drug close to the actuator orifice of a pressurized aerosol, the use of such sprays in the nose gives poor

Table 5

Oral peak expiratory flow			
Mean + SD	Budesonide	Placebo	<i>P</i>
Morning	497 + 74	458 + 92	0.02
Evening	495 + 71	480 + 89	0.09

drug distribution and a high deposition in Little's area of the septal wall (Locus Kiesselbach) (9), which is the origin of most nose bleeds. Only about 20 % of the steroid administered from a pressurized aerosol will reach the ciliated epithelium in the nose (11). An aqueous solution delivered from a metered-dose pump spray gives a better distribution pattern (10), with a 50 % deposition in the ciliated area (11).

In contrast to conventional delivery systems, only inhaled air was used to transport the drug particles to the site of action in the nose with the nasal inhalation system used in the present study. The complete absence of steroid-induced nasal side effects by this method indicates that nose bleeding, and probably also the rare septal perforations, can be avoided.

It is possible that this nasal inhalation system is useful in rhinitis patients who also have bronchial hyperreactivity and cough as an asthma equivalent. Their bronchial symptoms are often neglected or only treated with occasional use of a β_2 -agonist. However, the use of a conventional pressurized steroid aerosol directly in the nose may also cause a reduction in cough (4) and exercise-induced asthma (5).

In patients who only suffer from nasal symptoms our nasal inhalation system will result in an unnecessary deposition in the spacer device and in an unwanted deposition in the bronchi. A delivery system which exclusively gives deposition in the nose is preferable.

Table 6

Use of rescue medication			
Mean + SD	Budesonide	Placebo	<i>P</i>
Terbutaline spray	1.5 + 2.3	2.0 + 2.2	0.03
Antistin-Privin eye drops	1.2 + 1.6	1.8 + 2.5	0.15
Oxymetazoline nose drops	1.2 + 3.0	2.8 + 5.8	0.12
Terfenadine tablets	0.29 + 0.84	0.45 + 0.82	0.14

It is a potential hazard of the nasal inhalation system that bronchial drug deposition depends on nasal pathology, especially nasal blockage. However, only one of 15 nasal inhalations of a β_2 -agonist failed to cause bronchodilatation in another study (12), which also showed a high degree of correlation between the effect of nasal and oral inhalation. The same study showed that a 50% higher drug dosage was necessary to achieve a certain degree of bronchodilatation with nasal compared with oral inhalation. This indicates that in bronchial asthma, drug economy is not favoured by nasal inhalation. This negative aspect may be balanced by added efficacy on nasal symptoms and absence of oral side effects.

Infants with asthmatic bronchitis and bronchial asthma have not yet benefited from the progress in topical steroid therapy, as they are unable to cooperate with oral drug inhalation from metered-dose inhalers. It can be anticipated that infants will object to the insertion of an adaptor into the nostril, but a face mask will probably be acceptable (3).

In conclusion, we have shown that nasal inhalation of a steroid from a spacer device is effective in both rhinitis and asthma, but it is still an open question whether nasal inhalation can improve the ratio of anti-rhinitis/asthma effect versus side effects. The present study has indicated that the rate of side effects from nasal inhalation is absent or very low, but probably a higher steroid dosage is required for the treatment of rhinitis and asthma. Nasal steroid inhalation is potentially useful in patients with rhinitis and asthma who have local side effects

in the nose or the mouth/throat, and in infants who are unable to cooperate with oral inhalation.

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Table 7

Side effects

No. patients (No. days)	Budesonide	Placebo
Dry nose	8(45)	8(69)
Bleeding nose	3(5)	6(17)
Hoarseness	4(48)	6(57)
Nose irritation from spray	13(87)	14(123)
Mouth irritation from spray	2(15)	3(31)
Throat irritation from spray	4(32)	5(47)
Lung irritation from spray	3(30)	4(38)
Other adverse effects	1(13)	4(22)

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