

Nasal inhalation of budesonide from a spacer in children with perennial rhinitis and asthma

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The standard treatment of allergic rhinitis and asthma consists of topical corticosteroids administered intranasally and inhaled through the mouth. Although this therapy is highly effective, and side-effects are few and mild, it may be possible further to improve the therapeutic index and patient compliance with the treatment. In the present study, we evaluated a nasal inhalation system used for the simultaneous treatment of rhinitis and asthma. In principle, it results in an airway deposition of the corticosteroid similar to that of inhaled allergens. Twenty-four children with perennial rhinitis and asthma inhaled budesonide through the nose from a pressurized aerosol, attached to a spacer device, in a double-blind, placebo-controlled, crossover study. Compared with placebo, budesonide treatment resulted in a significant reduction of nasal symptoms ($P < 0.01$) and of asthma symptoms ($P < 0.05$), and in an increase of nasal peak inspiratory flow ($P < 0.001$) and of oral peak expiratory flow ($P = 0.01$). There were no differences between budesonide and placebo in local side-effects, such as dry nose, nosebleed, and hoarseness. We conclude that nasal inhalation of a corticosteroid from a spacer offers a simple and effective treatment for both rhinitis and asthma in children, but it is an open question whether the nasal inhalation system can improve the ratio of antirhinitis/asthma effects to side-effects.

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Normal persons, at rest, breathe exclusively through the nose, which is the natural entrance to the human airways. Particles in the inhaled air, such as allergens, are largely deposited in the nasal cavities, and to a lesser degree, in the bronchi (1). This implies that patients with inhalant allergy probably have allergic inflammation in the entire airway mucosa, whether they suffer from rhinitis, asthma, or both.

Topical corticosteroids are increasingly used for the treatment of rhinitis and asthma, allergic as well as nonallergic (2). In rhinitis, a relatively large amount of steroid is actively sprayed into the nose, resulting in an uneven distribution over the nasal mucosa (3, 4). Although local side-effects are usually mild and rare, they do occur (5, 6). In asthma, the steroid is inhaled through the mouth, and this can result in the development of oral candidiasis (7). Although this side-effect can largely be avoided by using a spacer device (8), oral inhalation, with a considerable and unnecessary drug

deposition in the first part of the gastrointestinal tract, is not appropriate in the treatment of a disease which is confined to the airways.

The present study aimed to test the hypothesis that nasal inhalation of a corticosteroid can be effective for both rhinitis and asthma in children. A deposition pattern which is similar for allergen and the anti-inflammatory drug seems appropriate to treat inflammation throughout the airways, and to obtain the best ratio of wanted antirhinitis/asthma effects to local adverse effects. In addition, the use of only one spray and one inhalation for the treatment of two diseases is likely to improve patient compliance. In this study, we used nasal inhalation of budesonide delivered from a pressurized aerosol into a spacer device equipped with a nozzle. Morén & Newman (9) have shown that this nasal inhalation system results in deposition both in the nose and in the bronchi, and we have earlier shown this system to be efficacious in adults with seasonal allergic rhinitis and asthma (10).

Material and methods

Study design

The study design was placebo-controlled and double-blind with a crossover technique. Children with perennial rhinitis and asthma were allocated at random to receive either budesonide for 3 weeks (period 1) followed by placebo for 3 weeks (period 2), or the reverse. The first 2 weeks in each period acted as a washout period, and only symptoms and airway function tests during the last week of each treatment period were used as effect parameters.

Patients

The study comprised 24 children with both perennial rhinitis and asthma, allergic and nonallergic. The diagnosis of asthma was certified by a $\geq 20\%$ increase in FEV₁ after the inhalation of a β_2 -agonist. The children's mean age was 11.3 years (range 8–15 years); nine girls and 15 boys. They all suffered from daily symptoms of the nose and bronchi, and they received treatment with topical corticosteroids in a dose of 200–400 μg once daily in the nose, and a dose of 200–400 μg twice daily in the bronchi (mean daily dose of inhaled corticosteroid: 646 μg). Patients and parents gave informed consent for the participation in the study, and the protocol was approved by the Ethics Committee of Copenhagen.

Medication

Test medication, consisting of budesonide pressurized aerosols, delivering 50 or 200 μg per actuation, and identical placebo aerosols were supplied by Astra Draco, Lund, Sweden. Each patient received an individual dose which was double the dose of inhaled budesonide used for the treatment of asthma (that is, a study dose of 800–1600 μg daily, mean 1292 μg). The reason for doubling the dose was that an earlier study had indicated less bronchial drug deposition from nasal than oral inhalation (11). The total dose was divided into two doses, morning and evening. The aerosol was inhaled from a 0.75-l, pear-shaped spacer device (Nebuhaler®) equipped with a nozzle specially made for the present study (Fig. 1). The patients were instructed to check nasal patency and to inhale only through a patent nostril. After a deep expiration, they were instructed to take a slow (2 s), maximal nasal inhalation through the device, with the other nostril closed, and to hold the breath for about 10 s. The procedure was then repeated in the other nostril. The patients were allowed to use their ordinary β_2 -agonist inhaler as needed.

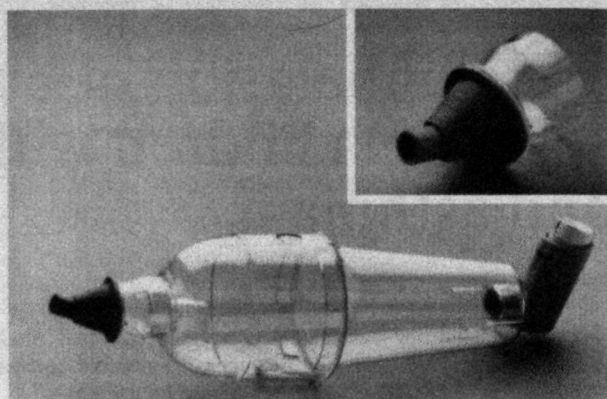


Fig. 1. Pear-shaped spacer device (Nebuhaler®) equipped with nozzle, used for nasal inhalation of budesonide.

In-office measurement of airway function

The patients measured nasal peak inspiratory flow (NPIF) (best of three) with a Youlton Peak Nasal Inspiratory Flow Meter, and peak expiratory flow (PEF) through the mouth (best of three) with a Mini-Wright Peak Flow Meter at visits to the hospital as close as possible to the end of each of the two treatment periods. In addition, subjects were asked about possible side-effects (dry nose, nosebleed, hoarseness, or other symptom), and about their severity (0 = none; 1 = mild; 2 = moderate; 3 = severe).

Daily measurement of airway function and recording of symptoms

The patients measured NPIF and oral PEF morning and evening on a daily basis. The patients/parents filled in a diary card every evening and graded nasal and bronchial symptoms from 0 (worst) to 4 (best). The number of puffs used from the β_2 -inhalers was also noted.

Statistics

Effect of treatment, effect of period sequence, and carry-over effect were analyzed by unpaired *t*-tests. All *P* values were two-sided, and the significance level of the statistical test was 5%.

Results

There were no significant differences between the two treatment groups in demographic data (Table 1). One patient in the placebo-budesonide group discontinued prematurely during the first treatment period for personal reasons. Otherwise, no data were excluded from the analysis.

Table 1. Demographic data in two treatment groups (mean $\pm$ SEM) ($P>0.05$ for all parameters)

	Budesonide-placebo	Placebo-budesonide
Age	10.6	12.0
Height (cm)	142	150
Weight (kg)	36.8	43.9
Prescribed dose of budesonide (μ g)	1300	1283

Table 2. In-office measurements of NPIF at end of each treatment period (l/min; mean $\pm$ SEM) ($P<0.001$)

	Period 1	Period 2
Budesonide-placebo	184 $\pm$ 20.6	161 $\pm$ 21.4
Placebo-budesonide	115 $\pm$ 15.8	181 $\pm$ 14.6

Table 3. In-office measurements of oral PEF at end of each treatment period (l/min; mean $\pm$ SEM) ($P=0.01$)

	Period 1	Period 2
Budesonide-placebo	360 $\pm$ 20.8	326 $\pm$ 26.1
Placebo-budesonide	373 $\pm$ 25.6	406 $\pm$ 25.7

Table 4. Home measurements of NPIF in morning during last week of each treatment period (l/min; mean $\pm$ SEM) ($P<0.05$)

	Period 1	Period 2
Budesonide-placebo	160 $\pm$ 19.0	158 $\pm$ 18.3
Placebo-budesonide	117 $\pm$ 13.2	153 $\pm$ 18.7

The in-office measurements of NPIF, at the end of the two treatment periods, showed a fall in the budesonide-placebo group and an increase in the placebo-budesonide group (Table 2). There was no statistically significant carry-over effect, but there was an effect of period ($P=0.007$), probably because the children had improved their skill in the unusual technique of NPIF measurement.

The data for oral PEF also showed a fall in the budesonide-placebo group and an increase in the placebo-budesonide group (Table 3). There was no statistically significant carry-over effect or effect of period.

Daily home measurements of NPIF and of oral PEF in the morning and in the evening during the last treatment week in each period confirmed the results of the in-office measurements (Tables 4–7).

The mean symptom scores during the last week of each treatment period showed a decrease (condition aggravated) in the budesonide-placebo group and an increase (condition improved) in the placebo-budesonide group for both rhinitis (Table 8) and asthma (Table 9).

There were no differences in the use of β_2 -inhalers in the two treatment groups (Table 10). Local side-effects were few and mild, and there were no differences between budesonide and placebo treatment (Tables 11–13).

Table 5. Home measurements of NPIF in evening during last week of each treatment period (l/min; mean $\pm$ SEM) ($P=0.01$)

	Period 1	Period 2
Budesonide-placebo	165 $\pm$ 19.5	162 $\pm$ 18.6
Placebo-budesonide	117 $\pm$ 12.7	153 $\pm$ 17.7

Table 6. Home measurements of oral PEF in morning during last week of each treatment period (l/min; mean $\pm$ SEM) ($P<0.05$)

	Period 1	Period 2
Budesonide-placebo	337 $\pm$ 20.9	322 $\pm$ 23.0
Placebo-budesonide	366 $\pm$ 22.1	378 $\pm$ 29.0

Table 7. Home measurements of oral PEF in evening during last week of each treatment period (l/min; mean $\pm$ SEM) ($P=0.05$)

	Period 1	Period 2
Budesonide-placebo	342 $\pm$ 21.8	322 $\pm$ 22.7
Placebo-budesonide	370 $\pm$ 23.2	378 $\pm$ 22.2

Table 8. Score for rhinitis symptoms (0 worst and 4 best) during last week of each treatment period (l/min; mean $\pm$ SEM) ($P<0.01$)

	Period 1	Period 2
Budesonide-placebo	2.33 $\pm$ 0.45	1.50 $\pm$ 0.32
Placebo-budesonide	0.91 $\pm$ 0.31	3.18 $\pm$ 0.26

Discussion

The present study has shown that nasal inhalation of the corticosteroid budesonide from a spacer can have a beneficial effect on both rhinitis and asthma in children. This confirms the results of an earlier study using the same inhalation system in adult patients with pollen-induced rhinitis and asthma (11).

A number of studies have shown that intranasal application of corticosteroids from a pressurized aerosol (12, 13) and from an aqueous pump spray (14, 15) have some beneficial effect on asthma symptoms. As the direct application of a nasal spray does not result in any significant deposition of the drug in the lower airways (9), the effect on asthma symptoms is probably due to an immunologic interaction between upper and lower airways (16). The effect of simple intranasal drug application, however, has not been marked, as, for example, in the study by Henriksen & Wenzel (12), in which treatment had an effect on exercise tolerance, but not on peak flow. On the other hand, the antiasthma effect of nasal inhalation from a spacer in our study showed a highly significant effect on both asthma symptoms and peak flow. There is little doubt that this added efficacy was due to bronchial drug deposition with the nasal inhalation system used in the present study (9, 10).

Due to the high linear velocity of an aerosolized drug close to the actuator orifice of a pressurized canister, the use of such sprays in the

Table 9. Score for asthma symptoms (0 worst and 4 best) during last week of each treatment period (l/min; mean $\pm$ SEM) ($P < 0.05$)

	Period 1	Period 2
Budesonide-placebo	2.67 $\pm$ 0.31	2.08 $\pm$ 0.42
Placebo-budesonide	1.09 $\pm$ 0.42	3.27 $\pm$ 0.24

Table 10. Number of puffs from β_2 -inhaler during last week of each treatment period (l/min; mean $\pm$ SEM) ($P > 0.05$)

	Period 1	Period 2
Budesonide-placebo	1.22 $\pm$ 0.68	1.34 $\pm$ 0.66
Placebo-budesonide	2.72 $\pm$ 0.75	2.09 $\pm$ 0.83

Table 11. Side-effect scores for dry nose during last week of each treatment period (mean) ($P > 0.05$)

	Period 1	Period 2
Budesonide-placebo	0.18	0.11
Placebo-budesonide	0.29	0.13

nose gives a poor drug distribution and a high deposition in Little's area of the septal wall (locus Kieselbachi) (5), which is the origin of most nosebleeds. Only about 20% of the corticosteroid administered from a pressurized aerosol reaches the target for the treatment, i.e., the ciliated epithelium (4). An aqueous solution delivered from a metered-dose pump spray gives a better distribution pattern (3) with 50% deposition in the ciliated area (4). Preliminary data (9) indicate that there is a more uniform intranasal drug distribution from the nasal spacer system, which uses only inhaled air for transportation of the drug to the site of action.

Although local side-effects are usually mild when conventional intranasal sprays are used, they do occur (6). It seems likely that our inspiration-driven spacer system, causing no direct drug impaction on the nasal mucosa, is associated with even less risk of local side-effects. In the present study, budesonide did not cause more nose dryness or nosebleeds than placebo, but the treatment period was too short to allow a reliable evaluation of the incidence of local side-effects.

It can be argued that, in asthma, it is a potential hazard of the nasal inhalation system that bronchial drug deposition depends upon nasal disorder, especially nasal blockage. However, only one out of 15 nasal inhalations of a β_2 -agonist failed to cause bronchodilation in an earlier study (10), which also showed a high degree of correlation between the effect of nasal and of oral inhalation from a spacer. Neither in the present study nor in our former study (16) does it seem to have been a problem for the patients to find a moment with a patent nostril to inhale the drug. In addition, the nasal corticosteroid deposition opens a blocked nose.

Table 12. Side-effect scores for nosebleed during last week of each treatment period (mean) ($P > 0.05$)

	Period 1	Period 2
Budesonide-placebo	0.02	0.01
Placebo-budesonide	0.01	0.00

Table 13. Side-effect scores for hoarseness during last week of each treatment period (mean) ($P > 0.05$)

	Period 1	Period 2
Budesonide-placebo	0.17	0.07
Placebo-budesonide	0.15	0.04

We have earlier found that a 50% higher drug dosage is necessary to achieve a certain degree of bronchodilation with nasal inhalation than with oral inhalation of a β_2 -agonist (10). This indicates that drug economy may not favor a nasal inhalation system in patients who exclusively suffer from bronchial asthma. This negative aspect may, in some patients, be balanced by the total absence of oral side-effects, and, in theory, by the inhibition of upper airway inflammation, which may have an effect on lower airway inflammation and asthma.

In the present study, we wanted to test a new therapeutic principle, which may or may not be useful in the future. Our results cannot be used to support a change in clinical practice, because dose-effect and dose side-effect profiles have not been analyzed. The total dose of corticosteroid used was high and may be associated with a risk of systemic side-effects during long-term treatment, especially because a dose nasally inhaled and absorbed may have more systemic activity than an orally inhaled dose (17, 18).

In conclusion, we have shown that nasal inhalation of a corticosteroid from a spacer device is effective in the treatment of both perennial rhinitis and asthma in children. However, it is still an open question whether our nasal inhalation system can improve the ratio of antirhinitis/antiasthma effects to side-effects.

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