

Simultaneous treatment of rhinitis and asthma by nasal inhalation of corticosteroid from a spacer

Authors' affiliations:

N. Mygind, R. Dahl, Department of Respiratory Diseases, Aarhus University Hospital, Aarhus
H. Bisgaard, Department of Paediatrics, Rigshospitalet, Copenhagen, Denmark

Correspondence to:

Niels Mygind MD
Department of Respiratory Diseases
Aarhus University Hospital
DK-8000 Aarhus
Denmark

Introduction

Normal persons, at rest, breathe exclusively through the nose, which is the natural entrance to the 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 used increasingly for the treatment of rhinitis and asthma, allergic as well as nonallergic (2). In rhinitis, a relatively large amount of drug 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 corticosteroid is inhaled through the mouth, and this can result in the development of oral candidiasis (7). Although these side effects can largely be avoided by use of a spacer device (8), oral inhalation, with a considerable and unnecessary drug deposition in the first part of the gastrointestinal tract, is not logical in the treatment of a disease confined to the airways.

The aim of the present two studies was to test the hypothesis that nasal inhalation of a corticosteroid can be effective both for rhinitis and asthma in adults and in children. A deposition pattern, similar for drug and for allergen, seems logical in order to treat inflammation in the entire airways. In addition drug deposition, confined to the diseased tissues, may give the best ratio between wanted anti-rhinitis/anti-asthma effects and local adverse effects. Finally, the use of only one spray for the treatment of two diseases is likely to improve patient compliance.

We have developed and studied an inhalation system for the simultaneous treatment of rhinitis and asthma. It

Date:

Accepted for publication 13 August 1998

To cite this article:

Mygind N., Bisgaard H. & Dahl R. Simultaneous treatment of rhinitis and asthma by nasal inhalation of corticosteroid from a spacer. *Allergy* 1999; 54, Suppl 57, 132–135.

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ISSN 0105-4538

consists of nasal inhalation of budesonide delivered from a pressurized aerosol into a spacer device equipped with a nozzle. It has been shown that this nasal inhalation system results in deposition both in the nose and in the bronchi (9).

Patients and methods

Study design

The study design was placebo-controlled and double-blind with a cross-over technique. Test medication consisted of pressurized aerosols, delivering budesonide or placebo. The patients took inhalations through both nostrils twice daily. The aerosol was inhaled from a pear-shaped spacer device (Nebuhaler) equipped with a nozzle. Patients completed diary cards and graded nasal and bronchial symptoms as well as local side effects. They also measured nasal inspiratory peak flow and oral expiratory peak flow. Use of rescue medication was recorded.

Study 1

Thirty adults (mean age 25.5 years) with grass-pollen allergy, who had rhinitis in the pollen season and also asthma, during at least one of the last five seasons, were included in the study. After a 10-day run-in period, the patients were allocated to two 14-day treatment periods with either placebo-budesonide or budesonide-placebo treatment. The dosage of budesonide was 800 µg a day, given as two inhalations of 100 µg through each nostril twice daily.

Study 2

Twenty-four children (mean age 11.3 years) with both perennial rhinitis and asthma were included in the study. Before the trial they all received treatment with topical corticosteroids in a dose of 200–400 µg once daily in the nose and twice daily in the bronchi. They were allocated to receive either budesonide for 3 weeks (period 1) followed by placebo for 3 weeks (period 2), or the reverse. Each patient received an individual dose which was the double of the dose of inhaled budesonide used for the treatment of asthma. The daily study dose varied from 800 to 1600 µg with a mean of 1292 µg. It was divided into two doses, morning and evening.

Results

The results from these two studies have been published previously in detail (10, 11).

Study 1

In the adults with pollen-induced rhinitis and asthma, there was a highly significant difference between budesonide and placebo periods with regard to nasal peak flow ($P=0.0003$) (Table 1). Measurement of oral peak flow showed a less marked difference between the two treatment periods ($P=0.02$).

There was a clear preference for active treatment with regard to nasal symptoms ($P=0.005$) and bronchial symptoms ($P=0.005$), but not eye symptoms.

The use of rescue medication for nasal symptoms showed a non-significant trend in favour of active treatment.

Local side effects were few and mild, and there were no differences between budesonide and placebo treatment.

Study 2

In children with perennial rhinitis and asthma, the in-office measurements of nasal peak flow and of oral peak flow at the end of the two treatment periods showed a fall in the budesonide-placebo group and an increase in the placebo-budesonide group (Tables 2, 3). Daily home measurements of peak flow confirmed the results of the in-office measurements.

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 3) and asthma (Table 4).

There were no differences in the use of beta₂-inhalers in the two treatment groups.

Local side effects were few and mild, and there were no differences between budesonide and placebo treatment.

Discussion

A number of studies have shown that intranasal application of a corticosteroid from a pressurized aerosol (12, 13) and from an aqueous pump spray (14, 15) has a beneficial effect on asthma symptoms. As the direct application of a nasal spray does not result in any significant deposition of the drug

Table 1. Adults with pollen-induced rhinitis and asthma. In-office measurements of NPIF at the end of each treatment period (mean ± SEM) ($P=0.0003$) (10)

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

in the lower airways (9), the effect on asthma symptoms is due probably to an immunological/inflammatory interaction between upper and lower airways (16).

In contrast to a pressurized aerosol used directly in the nose, the nasal inhalation system used in the present studies results in corticosteroid deposition in the lower airways. Morén and Newman (9) found deposition in both nose and bronchi when radioactively traced 3 µm large particles were inhaled through the nasal spacer system. We have earlier, by measuring the bronchodilator response, shown indirectly bronchial deposition of a beta₂-agonist aerosol inhaled through the nose with the same spacer system (17). It is therefore reasonable to assume that bronchial deposition of budesonide is, at least in part, responsible for the pronounced anti-asthma effect obtained in the present studies.

Due to the high linear velocity of an aerosolized drug close to the actuator office of a pressurized canister, the use of a pressurized aerosol in the 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 nose bleeds. Only about 20% of the corticosteroid administered from a pressurized aerosol will reach the target for the treatment, which is the ciliated epithelium (4). An aqueous solution, delivered from a metered-dose pump spray, gives a somewhat better distribution pattern (3), with a 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 inspiratory-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 studies, budesonide did not cause more mucosal dryness or nose bleeding than placebo. However, the treatment period was too short to give a reliable evaluation of the incidence of local side effects.

Table 2. Children with perennial rhinitis and asthma. In-office measurements of oral PEF at the end of each treatment period (mean ± SEM) ($P=0.01$) (11)

Budesonide–placebo	Placebo–budesonide
Period 1 360 ± 20.8	373 ± 25.6
Period 2 326 ± 26.1	406 ± 25.7

Table 3. Children with rhinitis and asthma. Score for rhinitis symptoms (0 worst and 4 best) during the last week of each treatment period (mean ± SEM) ($P<0.01$) (11)

Budesonide–placebo	Placebo–budesonide
Period 1 2.33 ± 0.45	0.91 ± 0.31
Period 2 1.50 ± 0.32	3.18 ± 0.26

In patients who suffer exclusively from rhinitis a delivery system which confines drug deposition to the nose may be preferable to the nasal spacer system, which gives an unnecessary drug deposition in the bronchi. However, hypothetically some bronchial deposition of corticosteroid may prevent the development of asthma. It is possible that the nasal spacer inhalation system can be 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 beta₂-agonist. Finally, it is possible that suppression of bronchial inflammation may be necessary in order to control severe rhinitis. Greiff and coworkers (17) have, in a recent study of pollen allergy, shown a clear anti-rhinitis effect of orally inhaled budesonide. It is, however, not clear whether the mode of action is an immunological/inflammatory link between upper and lower airways, or whether it is due to absorption of the corticosteroid.

It can be argued that, in asthma, it is a potential hazard of the nasal inhalation system that bronchial drug deposition depends upon nasal pathology, especially nasal blockage. However, only one of 15 nasal inhalations of a beta₂-agonist failed to cause bronchodilatation in an earlier study (18), which also showed a high degree of correlation between the effect of nasal and of oral inhalation from a spacer. In the two present studies it does not seem to have been a problem for the patients to find a moment with a patent nostril for inhaling the drug. In addition, the nasal corticosteroid deposition will open up a blocked nose.

We have found previously that a 50% higher drug dosage is necessary to achieve a certain degree of bronchodilatation with nasal inhalation compared with oral inhalation (17), which indicates that drug economy may not be in favour of a

Table 4. Children with perennial rhinitis and asthma. Score for asthma symptoms (0 worst and 4 best) during the last week of each treatment period (mean ± SEM) ($P<0.05$) (11)

Budesonide–placebo	Placebo–budesonide
Period 1 2.67 ± 0.31	1.09 ± 0.42
Period 2 2.08 ± 0.42	3.27 ± 0.24

nasal inhalation system in patients who suffer exclusively from asthma. This negative aspect may, in some patients, be balanced by a total absence of oral side effects and, in theory, by the inhibition of upper airway inflammation, which may have a beneficial effect on lower airway inflammation and asthma.

Due to their content of CFC gas and other additives, pressurized aerosols are now largely replaced by dry powder inhalers, containing only the drug. One of us (HB) has recently described an automatic actuation of a dry powder inhaler (Turbuhaler) into a nonelectrostatic spacer for the use in young children (19). It is an important question, deserving further studies, as to whether optimal usage of this inhaler system with a corticosteroid is achieved by oral or by nasal inhalation.

Conclusions

In conclusion, we have shown that nasal inhalation of a corticosteroid from a spacer device is effective in the treatment of both rhinitis and asthma in adults and in children. The results also indicate that the incidence of local side effects is very low. However, it is still an open question as to whether our nasal inhalation system can improve the ratio between anti-rhinitis/anti-asthma effects and side effects, and whether it can improve patient compliance and reduce the cost of treatment. The nasal inhalation system may be particularly useful in patients with rhinitis and asthma, who suffer local side effects in the nose and/or in the mouth/throat from ordinary inhalation systems.

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