

Reduction of Metacholine-Induced Nasal Secretion by Treatment with a New Topical Steroid in Perennial Non-Allergic Rhinitis

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The value of three objective tests of the nasal mucosa in 22 patients with perennial non-allergic rhinitis treated with a topical corticosteroid has been investigated. Placebo and three different dosages of a new steroid, budesonide, were administered intranasally using a double-blind, cross-over technique. Nasal airway resistance was not reduced by the steroid treatment as compared with the placebo treatment. Eosinophilia in nasal smears was reduced by budesonide. However, the value of this test was decreased by the fact that eosinophilia was found in less than 50% of the patients at the beginning of the trial. Metacholine-induced nasal secretion was significantly reduced by the budesonide treatment. Symptom scores for nasal obstruction, secretion and sneezing attacks were also significantly reduced by the steroid.

Key words: intranasal steroid treatment; nasal airway resistance; nasal eosinophilia; nasal metacholine challenge; perennial non-allergic rhinitis.

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CLINICAL ASPECTS

In a double-blind study a new topical steroid, budesonide, reduced the symptoms in 22 patients suffering from perennial non-allergic rhinitis. Three different daily doses; 50, 200 and 800 µg were given intranasally as a spray. However, no clear dose-response result was obtained. Three objective parameters were used to evaluate the effect of treatment; anterior rhinomanometry, eosinophilia in nasal smears, and metacholine-induced nasal secretion. It is supposed that metacholine challenge is a valuable objective parameter for the evaluation of treatment effects also in other kinds of rhinitis with hypersecretion.

The mechanisms behind perennial non-allergic rhinitis are largely unknown. This has also characterized the treatment. Several surgical and pharmacological approaches to relieve the complaints have been tried. Although certain patients are reported to be cured by e.g. Vidian neurectomy (8), the generally most successful treatment offered to this big group of patients seems to be topical corticosteroids. Beclomethasone dipropionate for intranasal use is one such well-documented steroid (e.g. 7, 9, 10,

11). Another steroid for topical use, budesonide, with high local activity and low systemic effects, has recently been synthesized (13). This steroid has not been used by patients with perennial non-allergic rhinitis before, and one aim of this trial was to investigate its effect on the symptoms of these patients.

In trials of this kind, there has been a lack of good objective parameters suitable for effect assessment. As shown by Borum (2), patients with perennial rhinitis react with nasal hyper-

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secretion to local metacholine challenge as compared with normal subjects. Therefore, another aim of this study was to find out whether metacholine-induced nasal secretion can be used in measuring therapeutical steroid effects in perennial rhinitis.

MATERIAL AND METHODS

Twenty-two patients, five males and 17 females between the ages of 20 and 68 years (mean age 42 years), participated in this study. All the patients had a history of perennial rhinitis with two or more of the symptoms nasal obstruction, nasal secretion, and sneezing attacks for at least 1 year. All the patients had negative prick test reactions to a panel of standard allergens. Analysis of IgE in serum (PRIST) showed values below 20 kU/l in nine patients and between 20 and 100 kU/l in 13 patients. According to the manufacturer, Pharmacia, values higher than 100 kU/l are to be expected in IgE-mediated reactions. None of the patients had bronchial asthma or nasal polyposis. Originally the study comprised 23 patients, but one of them could not continue the trial due to social reasons.

Either budesonide 50, 200 or 800 µg or placebo was given daily as pressurized aerosols with one puff into each nostril morning and evening. The trial was carried out with a double-blind, cross-over technique and the different preparations were given in randomized order. Before the treatment began, there was a run-in period of 2 weeks. Each preparation was then taken during 2 weeks. Treatment periods were separated by 1-week wash-out periods.

When the symptoms were too severe, the patients were allowed to take tablets of phenylpropanolamine (50 mg). No other medication was allowed.

Daily symptom scores were given by the patients for nasal obstruction and secretion according to the following scale: none: 0; mild: 1; moderate 2; and severe: 3. For sneezing attacks the scale was: none: 0; 1–5 attacks: 1; 6–15 attacks: 2; and more than 15 attacks a score of 3. Side effects and consumption of phenylpropanolamine tablets were also recorded daily.

The nasal mucosa was objectively tested by

examining nasal airway resistance, eosinophilia in nasal smears, and metacholine-induced nasal secretion. The tests were always performed in the order stated and undertaken once at the end of the first week of the run-in period and then on the day after each treatment period. At the same time, always in the morning (7–9 a.m.), a serum sample was drawn for the purpose of determining the cortisol level. The nose and mouth were examined, too. During these visits the patients also received a new aerosol-can.

Nasal airway resistance was determined by means of anterior rhinomanometry and calculations of the resistance of the total nose as described by Broms et al. (5). For clinical use results are expressed in cm H₂O/(l/s) and for statistical use in degrees. Wider angles correspond to higher levels of resistance. Before ing, the patients were resting in a sitting position for 30 min in order to adjust to the environment. Then they were tested in a sitting position. After 10 min in recumbency, they were tested in that position as well.

Nasal smears were taken from both nose cavities. If eosinophilic cells comprised more than 10% of the leucocytes, nasal eosinophilia was considered to exist.

Nasal secretion was induced by the intranasal delivery of 0.2 ml metacholine bromide solution in each nostril using a De Vilbiss No. 15 spray. A total of 0.4 ml containing 12 mg metacholine was given. The patient then bent his head forward, breathed through his mouth, and collected the secretion during 15 min holding a funnel under his nose. With a syringe connected to the funnel, the volume of the secretion could be determined. There was a pause of at least 10 min between the taking of the nasal smear and the metacholine test.

Serum cortisol was determined by using a radioimmunoassay (RIA) cortisol (¹²⁵I). The RIA kit was purchased from NEN, New England Nuclear®, USA.

STATISTICAL METHODS

The mean value of the last 3 days of the patients' symptom scores in each period was

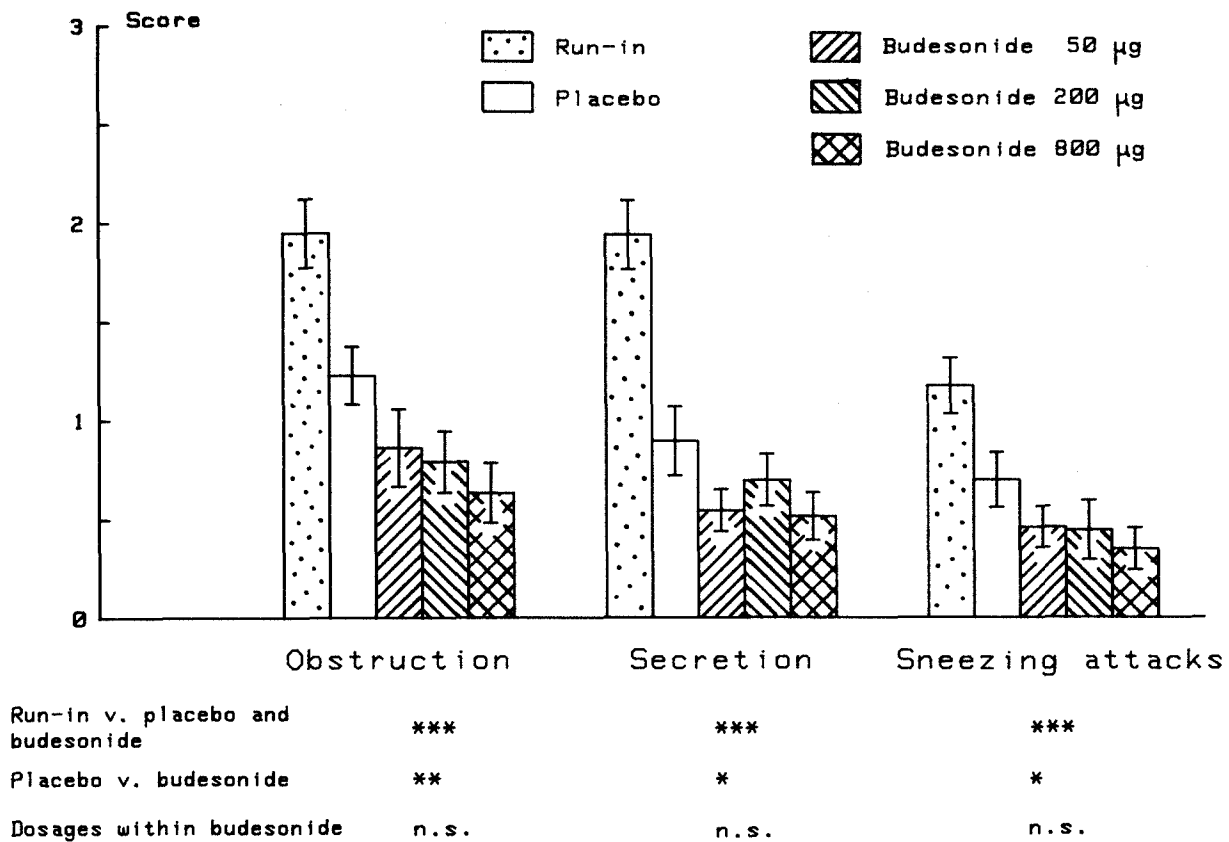


Fig. 1. Mean $\pm$ SEM for symptom scores. The number of patients is 19 for obstruction, 22 for secretion and 21. for sneezing attacks. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

used for the calculations. Three of the patients had no nasal obstruction at all throughout the trial and were therefore excluded from the evaluation of this symptom. For a similar reason, one patient was excluded from the evaluation of sneezing attacks. A two-way analysis of variance with orthogonal comparisons was used in analysing symptom scores, rhinomanometry assessments and serum cortisol levels. Metacholine secretion was analysed with Wilcoxon's signed rank sum test. By means of McNemar's test, eosinophilia in the run-in period was compared with eosinophilia during the last treatment period. In any test of significance, a two-sided alternative was used. $P > 0.05$ was considered as non-significant (n.s.), and $P < 0.05$ as significant.

RESULTS

Fig. 1 shows the mean symptom scores $\pm$ SEM of the run-in period and the treatment periods. For all three symptoms the average score in the treatment periods (placebo and different dos-

ages of budesonide) differed significantly ($P < 0.001$) from the score during the run-in period. Budesonide was significantly more active than placebo with regard to any symptom. The highest dosage of budesonide gave the lowest score in all symptoms. However, no significant differences were established between the budesonide dosages.

Some of the patients had to take phenylpropanolamine tablets during the trial. The mean consumption per day and patient was low. During the run-in periods it was 0.39 tablets, in the wash-out periods 0.10, and in the treatment periods 0.05 tablets.

Six patients reported side effects during the trial. Nose bleeding occurred in two patients, one being treated with 200 µg budesonide and the other with 800 µg. One patient reported headache with budesonide but also during a wash-out period. No side effects were reported during placebo treatment.

Of the objective parameters, the nasal airway resistance was significantly lowered only when the results before treatment (run-in period) were compared with those obtained from all the

Table 1
Rhinomanometry: nasal resistance parameter v_2 (degrees)

	Mean $\pm$ SEM	
	Sitting	Recumbency
Run-in	49 $\pm$ 4	49 $\pm$ 5
Placebo	45 $\pm$ 4	45 $\pm$ 4
Budesonide 50 μ g	42 $\pm$ 4	41 $\pm$ 4
Budesonide 200 μ g	40 $\pm$ 3	39 $\pm$ 3
Budesonide 800 μ g	41 $\pm$ 4	40 $\pm$ 3
<i>Significances from analysis of variance</i>		
Run-in vs placebo and budesonide	$P < 0.05$	$P < 0.05$
Placebo vs budesonide	n.s.	n.s.
Dosages within budesonide	n.s.	n.s.

treatments, placebo included. The results and the variance analysis are given in Table 1. There were no differences in respect to nasal patency between the sitting and recumbent positions.

Nasal eosinophilia was present among 10 of the 22 patients in the run-in period. In no case was eosinophilia induced during the treatment periods. On the day after the first treatment period five patients had nasal eosinophilia, after the second period three patients, after the third one, and after the last treatment period two patients. The reduction of eosinophilia was significant ($P < 0.01$).

The metacholine-induced nasal secretion was significantly lowered by all the treatments as compared with the secretion induced during the

Table 2
Metacholine-induced nasal secretion (ml/15 min)

	Mean	Median	Median decrease relative to run-in	Median decrease relative to placebo
Run-in	0.89	0.59		
Placebo	0.56	0.33	0.18 ($P < 0.05$)	
Budesonide 50 μ g	0.38	0.31	0.42 ($P < 0.01$)	0.12 n.s.
Budesonide 200 μ g	0.31	0.35	0.42 ($P < 0.001$)	0.09 ($P < 0.05$)
Budesonide 800 μ g	0.29	0.20	0.37 ($P < 0.01$)	0.06 ($P < 0.05$)

Table 3.
Cortisol in serum (μ g %). Normal range 10–30

	Mean $\pm$ SEM
Run-in	21.03 $\pm$ 2.29
Placebo	17.62 $\pm$ 1.20
Budesonide 50 μ g	18.95 $\pm$ 1.43
Budesonide 200 μ g	19.90 $\pm$ 1.99
Budesonide 800 μ g	19.69 $\pm$ 1.94
<i>Significances from analysis of variance</i>	
Run-in vs placebo and budesonide	n.s.
Placebo vs budesonide	$P < 0.05$
Dosages within budesonide	n.s.

run-in period. Budesonide – in the dosages of 200 and 800 μ g daily – was also able to reduce the metacholine-induced secretion as compared with the placebo treatment; see Table 2.

Serum cortisol levels did not show any significant decrease from baseline values after 2 weeks of treatment with any of the budesonide dosages (see Table 3).

DISCUSSION

As the hitherto best treatment of perennial non-allergic rhinitis seems to be topical steroids, trials with new improved steroid derivates are called for. Budesonide is a new synthetic non-

halogenated glucocorticoid. When implanted into subcutaneously deposited cotton pellets in rats, it had a local anti-inflammatory potency comparable to, and a 4–7 times lower systemic glucocorticoid activity than, that of fluocinolone acetonide (13). In patients with chronic bronchial asthma, the inhalation of budesonide in a dose of 1000 µg significantly reduced the peak expiratory flow resistance during 2 to 12 h after the administration (6).

The first aim when investigating new substances is to find out whether the drug can reduce symptoms. For each symptom, budesonide reduced the scores more than placebo in the present study. The next important task is to find the lowest effective dose. In this respect, however, no clear answer could be obtained. In another study of a similar group of patients treated with topical beclomethasone dipropionate (11), prolonged effects, i.e. effects remaining many days after the treatment was given, occurred. By arranging wash-out periods of 1 week each, and by calculating scores from the last 3 days of treatment only, the present study attempts to reduce the influence of possible prolonged effects on the statistical comparisons. The metacholine test indicates, however, that prolonged effects may exist even with these precautions.

The frequency of local side effects was roughly the same as the low nose-bleeding incidence with topical beclomethasone dipropionate aerosol (9, 11). No suppression of the serum cortisol level occurred with budesonide, as compared with assessments made in non-treatment periods.

With regard to rhinomanometry, no differences could be shown to exist between placebo and budesonide, or between the different budesonide dosages. To this group of patients, rhinomanometry therefore seems to be of little value as a method for controlling the effects of topical steroids. This is hardly surprising, as the nasal mucosa of this type of patients is known to change its thickness very easily under the influence of emotions, temperature changes, and so forth. The nasal airway resistance was not, as in normal subjects (4), higher in recumbency than in a sitting position. This was an unexpected

finding, particularly as many patients with perennial rhinitis suffer badly from nasal obstruction when lying down.

Nasal eosinophilia is found in 11% of normal subjects (12). In the present trial about half of the patients had nasal eosinophilia before treatment, which is about the same as the proportion found in a previously investigated group of similar patients (11).

It is well known that the human eosinophil leucocyte is very sensitive to steroids (1), a fact that is also verified with this steroid.

For many years, metacholine challenge has been used as an objective test of bronchial hyperreactivity. It evokes a bronchoconstriction which can be revealed in the changes of FEV₁. This forms a good testing system suitable for measuring pharmacological effects. No similar system for testing nasal hyperreactivity has been developed, probably for the reason that nasal airway resistance, or nasal peak flow, is too greatly affected by simultaneously occurring changes in the nasal patency, changes evoked by other stimuli than metacholine. Hypersecretion is often the main symptom in different kinds of rhinitis, but difficulties in measuring the secretion are still a limiting factor with regard to clinical use. However, the method worked out by Borum (3), in which he uses metacholine to induce secretion, is simple and has an acceptable reproducibility. Most patients with perennial non-allergic rhinitis have been shown to have a hypersecretion when challenged with metacholine. The reason why metacholine induces nasal hypersecretion is not known. One hypothesis is that the nasal glands have an increased sensitivity to stimuli. Another possibility is that the glands are enlarged and increased in number. In addition, the locally applied metacholine might reach the glandular cholinergic receptors more easily than in a normal mucosa. Against this background, discussions as to why steroids reduce the metacholine-induced nasal secretion are even more hypothetical. They probably act by virtue of the well-known anti-inflammatory steroid effect, with reduction of oedema and permeability.

When we compare the results of the metacholine challenge with the two other objective

parameters, rhinomanometry and nasal eosinophilia, the metacholine test seems to be the most sensitive one. After improvements in the administration and recording methods, this test system is likely to be of even greater value when it comes to judging therapy effects in different kinds of rhinitis.

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