

Budesonide and Nasal Histamine Challenge

ULF PIPKORN

ENT-Department, Kärnsjukhuset, Skövde, Sweden

The possible mode of action of the lately demonstrated steroid effect on the immediate type allergic reaction was investigated. The influence of a topical steroid, budesonide, on the effects that released mediators have on the nasal mucosa was also studied. A nasal histamine challenge study was performed in a double-blind, cross-over fashion, a 1-week pretreatment with budesonide or placebo preceding the challenge. Symptoms were recorded by means of symptom score as well as objectively via rhinomanometry.

In contrast to a previous allergen challenge study, the steroid was found to have minimal effect on the histamine-induced nasal symptoms. It is therefore concluded that other modes of steroid action must also be involved in the steroid effect on the immediate type allergic reaction.

Key words: histamine challenge; intranasal steroid treatment; nasal challenge.

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Glucocorticosteroids have now been used in the treatment of allergic airway diseases for 30 years. The introduction of beclomethasone dipropionate (BDP) for local treatment of the nose in allergic as well as vasomotor rhinitis has facilitated the management of these conditions without risking any systemic side effects (8).

Other steroids with similar effects have been introduced recently; one of them is budesonide. In clinical trials, it has proved to be as effective as BDP in the treatment of allergic rhinitis. It has also been shown to be effective in vasomotor rhinitis (2, 13, 14).

Not until recently has the effect of corticosteroids on the immediate allergic (type 1) reaction been demonstrated in allergen challenge testing. In nasal allergen challenge, the effects of BDP given locally for 1 week or longer (11, 16), and of budesonide 1 week prior to an allergen challenge (15), are demonstrable.

The duration of the treatment prior to challenge seems to be of importance in demonstrating this effect on the immediate reaction. The effect might theoretically be due to a reduced release of mediators from mast cells at allergen

challenge and/or to an inhibition of the effect from released mediators.

Several mediators are released from mast cells when reagin-dependent reactions take place. The main part of the mediator action in the nasal immediate type reaction is attributed to histamine (8). Histamine provocation has previously been used in order to induce nasal hypersecretion, nasal blockage and sneezing (1, 3, 5).

Aim of investigation

The aim of the present experimental study was to find out whether 1 week of pretreatment with a topical steroid reduced the vascular and glandular effects induced by histamine provocation. Such an effect could be one explanation for the protective effect of steroids demonstrated in the course of nasal allergen-challenge testing.

The study was approved by the Ethical Committee of the Medical Faculty of the University of Gothenburg.

MATERIAL AND METHODS

The trial was conducted over a pollen-free period of 2 months in a double-blind randomized fashion. Fourteen patients participated. Budesonide or placebo was given for 1 week prior to each challenge. The pretreatment was preceded by a 2-week wash-out period.

Fourteen patients, nine males and five females, aged 21–38 years (mean age 33.5 years), with seasonal allergic rhinitis were included in the study. All of them were asymptomatic (out of season) but had a verified hypersensitivity to either of the two allergens birch and grass. Verification was established by means of a positive history, a positive skin-prick test and a positive nasal allergen challenge test. Patients with structural abnormalities such as septal deviations and nasal polyps were excluded from the study.

The nasal challenges were performed with a technique used in a previous study with allergen challenges in the nose (15). The nasal challenges were performed with a nasal pump spray used for delivering DSCG solution (Lomudal Nasal®). Each spray delivers 0.13 ml of fluid and has been shown to produce a widespread distribution of the given fluid into the nasal cavity (9). Only one nasal cavity was challenged in each patient in the course of repeated provocations.

A solution of histamine hydrochloride in 0.9% saline solution was used for the challenge. A series of dilutions from 0.01% up to 1% histamine hydrochloride was also employed.

Part of the evaluation of the symptoms obtained after the challenge was accomplished by means of symptom scoring. The number of sneezes were counted and graded 0–3 according to the following scale: 0 sneezes = 0, 1–5 sneezes = 1, 6–10 sneezes = 2 and more than 10 sneezes = 3.

Nasal blockage and secretion were estimated by the patient 15 min after the challenge. The following scale was used: 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms and 3 = severe symptoms.

A rhinomanometer was used in order to evaluate the nasal obstruction (No. 1, Mercury

Electronics Ltd., Scotland + X-Y writer Mingor type RE 501 Goerz Electro, England).

Anterior rhinomanometry was performed with the cavity challenge. The recordings follow the method described by Broms (4), which expresses the nasal airway resistance as the degree of the angle on the X-Y writer (flow – pressure curve).

Before the beginning of the actual trial, an optimal nasal response – in terms of rhinomanometry, an increase over 60° – but not a total nasal blockage was aimed at in each patient.

A series of dilutions commenced with 0.26 ml of 0.01% histamine hydrochloride. If no nasal response was recorded, stronger dilutions were given every 30 min until the desired nasal response was obtained. The last dose to be administered was then maintained in the repeated provocations throughout the trial. Thirteen out of the 14 patients gave the desired response after 2.6 µg of histamine hydrochloride. The remaining patient needed only 0.78 µg.

The following preparations were given intranasally:

1. Budesonide 200 µg morning and afternoon.
2. Placebo morning and afternoon.

The last dose was given 2 h before each challenge.

All preparations were identical in appearance and contained the same vehicle. No other drugs were allowed throughout the trial.

Statistical methods

The symptom scores and the rhinomanometric values obtained were analysed by means of Wilcoxon's signed rank sum test.

RESULTS

All 14 patients who entered the trial completed the two challenges, which resulted in a total of 28 challenges. All patients are included in the statistical evaluation.

The obtained symptom scores are presented in Fig. 1.

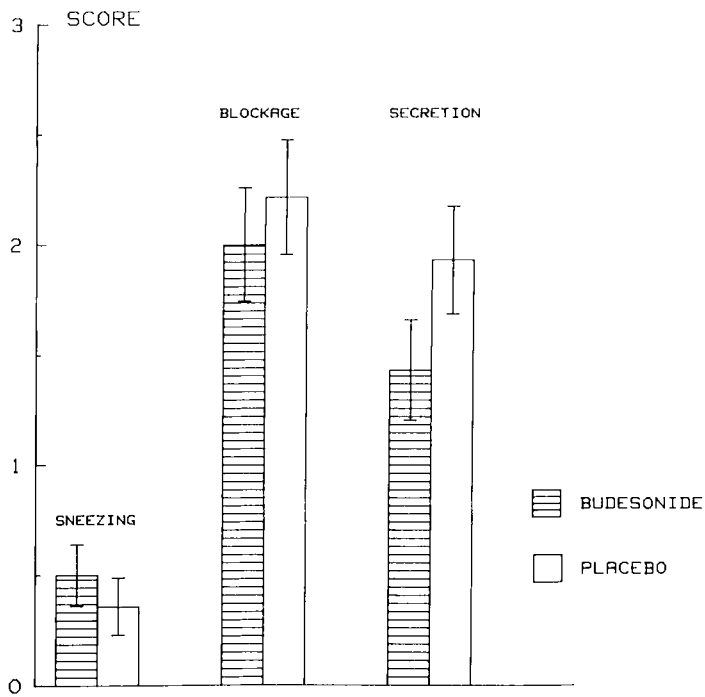


Fig. 1. Mean symptom score $\pm$ SEM. The maximum score is 3. The difference between active treatment and placebo is significant ($P < 0.05$) for secretion.

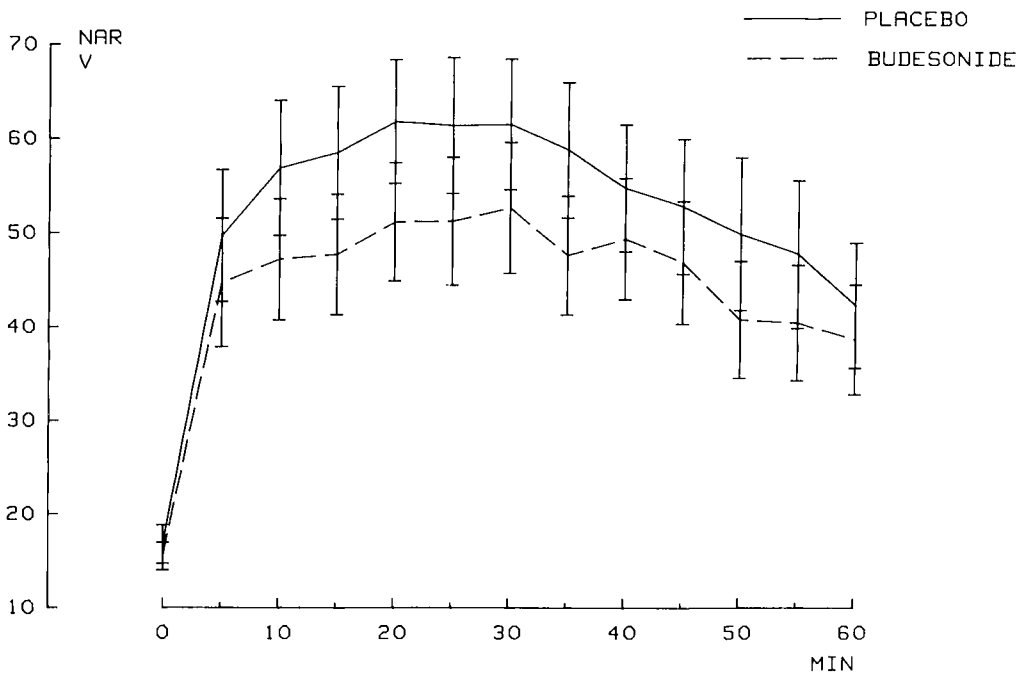


Fig. 2. Mean ($\pm$ SEM) of nasal airway resistance measurements. The difference is non-significant.

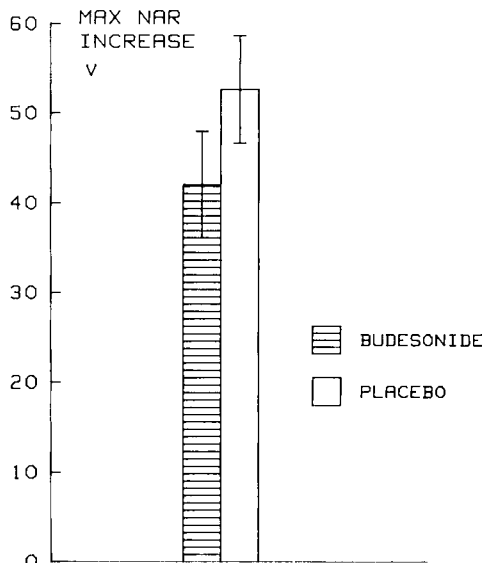


Fig. 3. Mean ($\pm$ SEM) of peak nasal airway resistance measurements. The difference is statistically significantly ($P < 0.05$) in favour of active treatment.

The number of sneezes recorded was very low in both groups and no difference was found, irrespective of treatment. Where nasal blockage and secretion were concerned a slightly lower score was recorded for the active treatment as compared with placebo. This difference was statistically significant ($P < 0.05$) regarding secretion.

The results from the nasal resistance measurements (NAR) are presented in Figs. 2 and 3. No difference in NAR was found before the histamine challenge. A slightly lower NAR was recorded after budesonide treatment over the 60 min of measurement after the challenge. The area under the curve and above the baseline did not differ statistically significantly between the two treatments. For individual peak measurements of the histamine-induced reaction, a statistically significant difference ($P < 0.05$) was found.

No adverse effects were noted after any of the pretreatments.

DISCUSSION

Although corticosteroids have been used in the treatment of allergic airway diseases for a long time, the mode of action of this treatment is not understood.

An effect of the immediate type reaction in allergen challenge tests has quite recently been shown after nasal treatment (of a week's duration or longer) with BDP (11, 16) as well as with budesonide (15). The mode of action of this recently demonstrated effect, which seems to be dependent on the duration of the pretreatment, is not understood either.

A reduction of the allergen-induced increase of basophilic cells in the nasal mucosa and nasal secretion has been demonstrated as a result of local treatment with BDP (12). This effect of steroid treatment has been shown in the early stages of treatment when the patient's disease already causes symptoms. The effect on basophils in patients whose disease produces no symptoms is not known.

Since the effect of steroids in allergen challenge testing has been demonstrated out of season, when the patients have no symptoms, it seems likely that other modes of action are involved. The aim of this study was to investigate whether the effect of steroids on the immediate type reaction could be attributed to a reduction of the effect of released mediators. Since the main part of the action of the mediators in the nasal immediate type reaction is attributed to histamine (8), histamine provocation was chosen for this study.

Nasal histamine provocations have previously been used experimentally to increase nasal secretion (5) as well as to induce nasal obstruction in order to evaluate nasal decongestants (1, 3).

The histamine-induced secretion is probably due to an indirect effect on the glands of the nasal mucosa through a parasympathic reflex (10). The histamine-induced nasal congestion seems to be a direct effect on the blood vessels in the mucosa (6).

In order to be able to compare the results from this study with the previous one, where the effect of budesonide on the immediate type

reaction was demonstrated (15), efforts were made to perform the challenges using the same procedure as in the previous study, the only difference being the use of histamine, not allergens, in the challenge.

Almost the same patients took part in both studies. Twelve of the 13 people who participated in the allergen challenge study also took part in the histamine challenge study. Only two additional persons were included. The same rhinomanometric reaction was aimed at in the pretrial challenges; this led to similar reactions after placebo treatments in the two studies.

The design of the studies was similar; a double-blind, cross-over technique was employed in both cases. The same doses and treatment periods of budesonide were used, and the wash-out periods were the same. Both studies were performed out of season.

In contrast to the allergen challenge study, the results obtained in the course of the present investigation show that budesonide had a very slight effect on the histamine-induced symptoms. The only statistical findings were a slight decrease of secretion and a reduction of the NAR peak after the challenge, as measured rhinomanometrically. This might be due to a "vasoconstrictor" effect on the nasal blood vessels similar to that demonstrated in dermal tests. Although the baseline values prior to the challenge were the same after placebo and active treatment using this technique, this effect might not be demonstrable until a challenge is performed.

This study demonstrated that there must be other modes of action involved in the effect of corticosteroids on the immediate type reaction. Further studies concerning the nasal mucosal histamine content and histamine release are in progress.

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Address:

Ulf Pipkorn
ENT-Dept.
Kärnsjukhuset
S-541 85 Skövde
Sweden

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