

Effect of corticosteroids on nasal blockage in rhinitis measured by objective methods

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This paper gives an overview of placebo-controlled studies of the effect of corticosteroid treatment on nasal blockage, based on objective measurements of nasal airway patency. A few studies of perennial rhinitis have indicated that pretreatment with an intranasal corticosteroid has a moderate effect on nasal hyperresponsiveness, measured as the histamine-induced increase of nasal blockage. Whereas the effect on allergen-induced early-phase symptoms is variable, the effect on the late-phase blockage is almost complete. In seasonal allergic rhinitis, a few studies have shown an effect of intranasal steroids on nasal airway resistance, nasal peak flow and on acoustic rhinometry, but there are no reports on the effect in adults with perennial rhinitis. In children with perennial disease, intranasal treatment results in increased nasal patency and, in one study, also in reduced mouth breathing and in an increased threshold for exercise-induced bronchoconstriction. In patients with nasal polyposis, intranasal steroids have an effect on nasal airway resistance and on nasal peak flow both before and after polypectomy. There is convincing evidence that intranasal corticosteroids provide a better effect than antihistamine on nasal blockage. Amazingly, there does not appear to be any report on the effect of systemic corticosteroid treatment on nasal airway patency, and it is therefore difficult to recommend this treatment in a rational dosage. In conclusion, there is a fairly good documentation in support of the efficacy of intranasal steroid treatment on nasal airway patency in rhinitis. An objective measurement of nasal airway patency ought to be the routine in controlled rhinitis trials.

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Topical corticosteroids

More than 100 double-blind placebo-controlled studies have – with one exception – shown efficacy of intranasal corticosteroids in allergic rhinitis, in non-infectious non-allergic rhinitis and in nasal polyposis (1). This treatment reduces symptom scores for sneezing, rhinorrhoea and nasal blockage. Blockage may be both a subjective feeling of discomfort and congestion and a reduced nasal airway patency. The correlation between subjective and objective parameters is variable (2), and this paper will exclusively deal with the effect of treatment on objective measurements of nasal airway patency, i.e. nasal airway resistance (NAR), nasal peak flow (NPF) – inspiratory (NPIF) and expiratory (NPEF) – and acoustic rhinometry (AR). Most of the placebo-controlled studies below have been performed with beclomethasone

dipropionate (BDP) (400 µg daily), budesonide (BUD) (400 µg daily) and fluticasone propionate (FP) (200 µg daily).

Postural vasomotor response

Nasal airway patency changes with body position and it is reduced when lying down. Hasegawa & Saito (3) showed that the postural variation of NAR was more marked in patients with allergic rhinitis than in normal controls and that this increased vasomotor response was reduced by treatment for 2 weeks with intranasal BDP. The mechanism behind this increased vasomotor responsiveness in allergic rhinitis is unclear and so is the mode of action of the topical steroid. An indirect effect on vasculature responsiveness, secondary to an anti-inflammatory effect, is more likely than a direct drug effect on blood vessels (4).

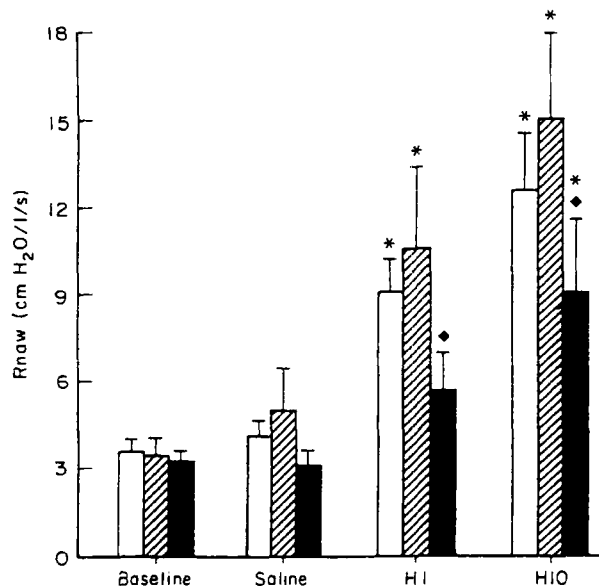


Fig. 1. Effect of beclomethasone dipropionate on histamine-induced rise in nasal airway resistance in perennial rhinitis. *= $P < 0.05$ vs. placebo; ace= $P < 0.05$ vs. placebo. Open bar=initial; hatched bar=placebo; filled bar=beclomethasone. H1=histamine 1 mg; H10=histamine 10 mg.

Histamine provocation test

Pipkorn (5) performed nasal histamine challenge in pollen-allergic patients outside the season. In contrast to a similar allergen challenge study (see below), BUD treatment for 1 week had minimal effect on the histamine-induced increase in NAR. Pipkorn, therefore, concluded that other modes of steroid actions must be involved in the steroid effect on the early-phase allergic response. These results are in contrast to those reported by Small & Barrett (6) who surprisingly found a better effect of intranasal steroid pretreatment on histamine-induced than on allergen-induced increase of NAR.

Because pollen-allergic patients, as a rule, may have normal nasal responsiveness outside the pollen season, it is clinically more relevant to study the drug effect in patients with perennial rhinitis who have nasal hyperresponsiveness. In a small study of eight patients, Studham et al. (7) found that pretreatment for 2 weeks with BDP had a significant protective effect on histamine-induced increase in NAR (Fig. 1). With a similar placebo-controlled design, Birchall et al. (8) found a 40% reduction in the histamine-induced increase in NAR when 11 patients with perennial rhinitis were treated with FP for 4 weeks. Thus, although the evidence is sparse, it indicates that intranasal steroid treatment can reduce vasomotor hyperresponsiveness in patients with perennial rhinitis.

Whereas bronchial responsiveness is usually studied merely at the bronchoconstrictor level,

nasal responsiveness can be studied at different levels: (a) a sensory nerve response (itching and sneezing), (b) a vasomotor response (NAR, NPF, AR), and (c) a secretory response (volume of secretion). The above studies seem to indicate an effect of intranasal corticosteroids on vasomotor responsiveness; and we have also found in an earlier study that BDP, in patients with perennial rhinitis, can reduce the afferent nerve sensitivity to a mechanical stimulus (9). In house-dust allergic patients, de Graaf-in 't Veld et al. (10) found a 41% reduction in histamine-induced sneezing and a 32% reduction in volume of secretion after treatment with FP for 2 weeks. Thus, intranasal corticosteroids seem to have an effect on several types of nasal hyperresponsiveness, but there is a definite need for more controlled studies.

Allergen provocation test

There is a series of controlled studies of the effect of intranasal steroids, given for 1–2 weeks, before allergen challenge. While some studies have shown a marked effect (11–14) others have merely found a marginal or mild effect on the early-phase response (15–17). This difference could be due to the mode and strength of the allergen challenge. All available data, on the other hand, show that the treatment almost completely inhibits the late-phase response. Whereas Grønborg et al. (17) found BUD to have a 17% reduction of early-phase change of NIPF, there was a 96% reduction of the late-phase blockage (Fig. 2).

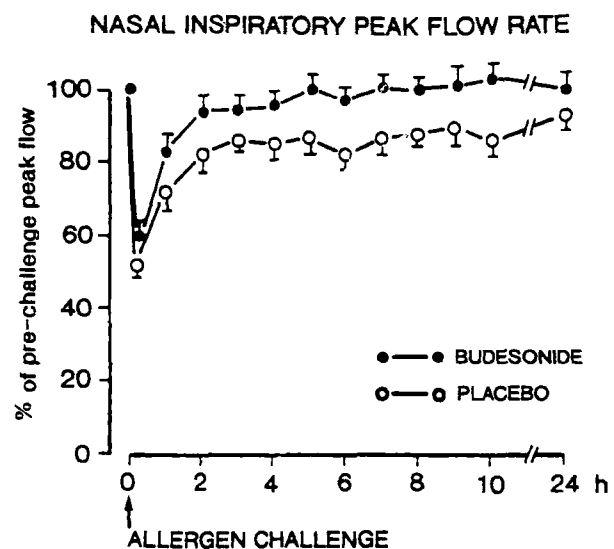


Fig. 2. Allergen-induced change in NIPF as a percentage of prechallenge values (mean $\pm$ SEM). From Grønborg et al. (17).

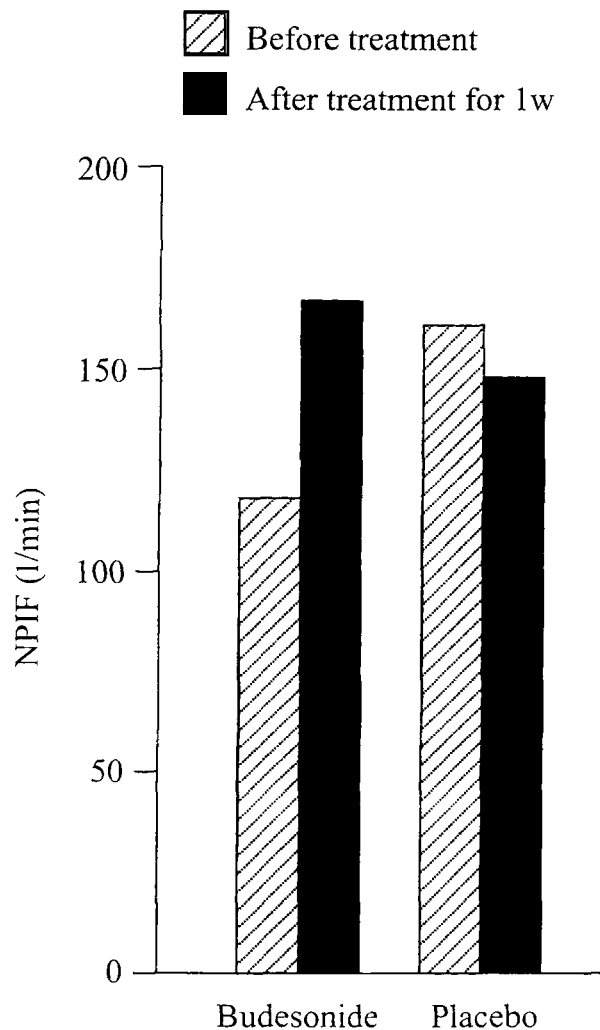


Fig. 3. NPIF (litres/minute) in patients with seasonal allergic rhinitis before and after 1 week of treatment with budesonide powder or placebo (budesonide vs. placebo, $P=0.007$). From Andersson et al. (19).

Seasonal allergic rhinitis

There are only a few hay fever studies in which nasal patency has been measured objectively during treatment with an intranasal corticosteroid. In 21 adult patients, there was a significant improvement in NAR in a group treated with triamcinolone acetonide when compared with a placebo group (87% vs 27%; $P<0.05$) (18). Andersson et al. (19), using BUD powder, showed a significant increase of NPIF during active treatment and a fall during placebo treatment ($P=0.007$) (Fig. 3).

A dose-effect study with FP in 423 patients showed a better effect of all three doses (25, 100 and 400 μg daily) than of placebo on symptom scores, but it was only the two highest doses which significantly reduced NAR (20).

Recently, Nielsen et al. (21) treated 27 patients with grass-pollen hay fever with FP or with placebo. Probably due to the low number of patients, there were no significant differences between the groups with regard to clinical parameters, including symptom score for nasal blockage ($P=0.1$). Nevertheless, there was a significant difference ($P<0.05$) between the two treatment groups with regard to acoustic rhinometry. Somewhat unexpectedly this difference was not shown by the measurement of nasal cross-sectional area but by the measurement of nasal volume. While the mean nasal volume in the placebo group decreased significantly, from before the season to the peak of the pollen season, it even tended to increase in the steroid group. The authors conclude that acoustic rhinometry as an objective method is sensitive in the assessment of nasal obstruction in rhinitis and of the impact of intranasal steroid therapy.

Perennial rhinitis in adults

We have not been able to find any placebo-controlled studies using objective methods for the measurement of nasal patency in adults with perennial rhinitis without polyps. This is amazing, because nasal blockage in chronic perennial rhinitis is considered to be a major indication for the use of intranasal steroids (22). In an open study of 60 adults with perennial rhinitis, FP (400 μg daily) had an effect on symptom scores for nasal blockage, but this could not be confirmed by the measurement of NAR (23).

Perennial rhinitis in children

Hynes et al. (24) studied intranasal BDP in children with non-purulent rhinitis, and found that rhinomanometry is more effective than symptom-atological or cytological assessment in making a distinction between a steroid group and a placebo group.

In another study, the efficacy of intranasal steroid treatment was assessed by anterior rhinomanometry in 44 children with perennial allergic rhinitis (25). NAR was significantly improved ($P<0.02$ vs baseline) in children receiving triamcinolone 82.5 $\mu\text{g}/\text{day}$ (33%) or 165 $\mu\text{g}/\text{day}$ (114%) but not in the placebo group (4%) (Fig. 4).

Interestingly, a study of children with chronic rhinitis, mouth breathing and asthma (26) showed that intranasal BUD, when compared with placebo, significantly decreased nasal obstruction ($P<0.05$), as well as NAR ($P<0.05$) and mouth breathing ($P<0.02$). The improvement in nasal obstruction correlated closely with the changes in mouth breathing (Fig. 5). Further, intranasally

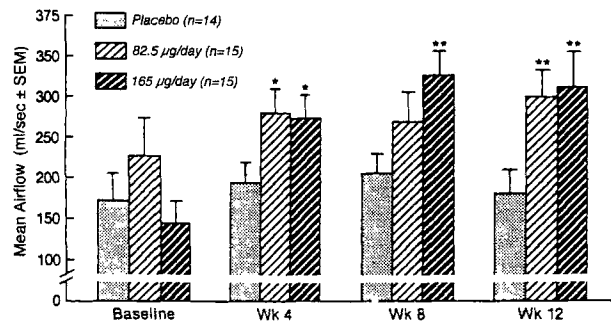


Fig. 4. Treatment of children with perennial allergic rhinitis with triamcinolone acetonide. Mean nasal airflow (ml/sec) for each treatment group at each evaluation visit. * $P < 0.05$ and ** $P < 0.02$. From Welch et al. (25).

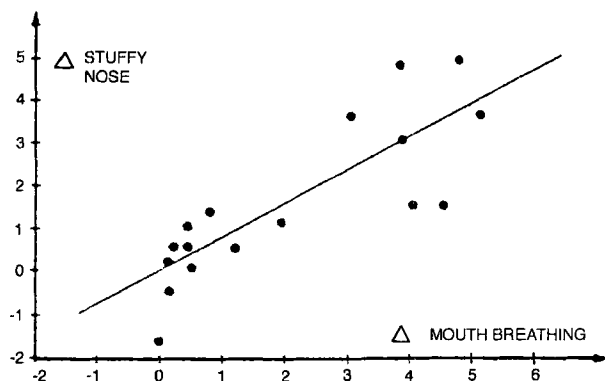


Fig. 5. Relationship between budesonide-induced changes in nasal obstruction and mouth breathing. Solid line is line of regression ($r = 0.80$, $P < 0.001$). From Henriksen et al. (26).

administered BUD resulted in less exercise-induced asthma and decreased cough, indicating that anti-inflammatory treatment of the nose can have a beneficial effect on hyperresponsiveness in the lower airways.

Nasal polyposis

Deuschl & Drettner (27) were the first to show a significant effect of intranasal steroid (BDP) on nasal airway patency (NAR). Holopainen et al. (28) measured NPF before and after a 4-month treatment with BUD or placebo, and, although the number of patients was low ($n = 19$), there was a significant difference in favour of steroid treatment ($P < 0.05$) (Fig. 6). Ruhno et al. (29) gave a high dosage of BUD (400 µg bidaily) to patients with nasal polyposis, and they found a highly significant reduction in nasal blockage and in NPIF as compared with placebo ($P = 0.0001$).

Drettner et al. (30) studied 22 patients for 3 months after polypectomy. Although there was a significant effect of flunisolide on the symptom score for stuffy nose, rhinomanometry failed to

show a significant difference between active and placebo treatment in this small study.

Virolainen & Puhakka (31) studied patients with nasal polyposis for 1 year after ethmoidectomy. The percentage of patients with normal NAR after 1 year was 68% in a BDP-treated group as compared with 33% in a placebo group.

Steroid molecules and delivery systems

In one study of 40 patients with allergic and vasomotor rhinitis (32), which employed anterior rhinomanometry, once daily triamcinolone acetonide (220 µg/day) and twice daily BDP (336 µg/day) nasal spray, given for 8 weeks, demonstrated equal efficacy in decreasing NAR (by 23% and 25%, respectively). There is another drug-comparative study in adult patients with perennial rhinitis, allergic and non-allergic, showing a slightly but significantly better effect on evening NPEF of BUD (400 µg) than of BDP (400 µg) (33).

Orgel et al. (34), in a double-dummy study, found a similar effect on NAR of BDP given from

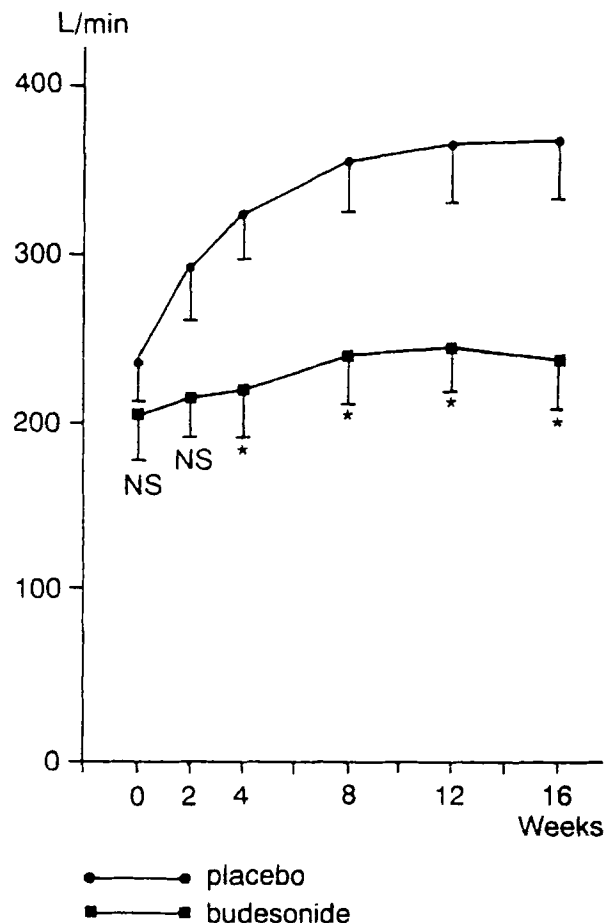


Fig. 6. Diagram showing mean nasal peak flow-SEM in patients treated with budesonide (circles) or placebo squares (* $P < 0.05$). From Holopainen et al. (28).

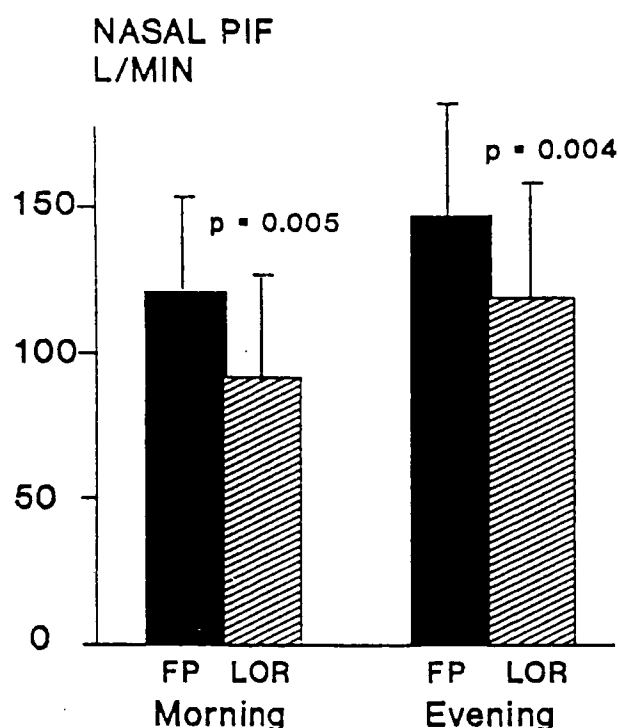


Fig. 7. NPIF (l/min) in patients with seasonal allergic rhinitis treated with either fluticasone propionate (FP) or loratadine (LOR). From Jordana et al. (37).

a pressurized aerosol and from an aqueous pump spray.

Comparison with antihistamine

Using allergen challenge as a model, Hilberg (35) found a significantly better effect of pretreatment with BUD than with terfenadine (120 mg) on allergen-induced increase of nasal airway patency within 1–2 hours after challenge, measured by acoustic rhinomanometry. The antihistamine, on the other hand, had a better effect on itching and sneezing. BDP aerosol produced significantly better control of the nasal obstruction in seasonal allergic rhinitis than did terfenadine (120 mg daily) when assessed by rhinomanometry (36). Jordana et al. (37) found a significantly better effect on morning and evening NPIF of FP than of loratadine (10 mg daily) in patients with ragweed allergy and seasonal allergic rhinitis (Fig. 7).

Systemic corticosteroids

Surprisingly, we have not been able to find any published placebo-controlled study on the effect of systemic corticosteroids on NAR, NPF or AR, but there is little doubt that this therapy is highly effective, as suggested by the studies below.

In an interesting study, Brooks et al. (38) evalu-

ated the relative contributions of vascular engorgement and the less reversible components (oedema, cellular infiltration) to production of allergic nasal congestion. In the pollen season, it was not possible to decongest symptomatic patients to baseline using only a topical vasoconstrictor, although this could be accomplished in those receiving oral methylprednisolone. Apparently, corticosteroid therapy relieved a non-vascular component of congestion, or it rendered vasoconstrictor therapy more effective.

Using a semi-objective and semi-quantitative recording of sneezing (number), nose-blowings (number) and nasal blockage (self-assessment) we have found a pronounced effect of systemic steroid (methylprednisolone 80 mg as a depot injection) on nasal blockage in seasonal allergic rhinitis, while the effect on sneezing and nose-blowings was merely shown by a reduced number of rescue medication with antihistamine tablets (39), indicating that systemic corticosteroid therapy is relatively more effective on nasal blockage than on sneezing and rhinorrhoea.

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