

Early and late nasal symptom response to allergen challenge

The effect of pretreatment with a glucocorticosteroid spray

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We challenged 30 pollen-sensitive volunteers with allergen, recorded symptoms and signs over a 10-h period, and rechallenged them after 24 h, in order to characterize the early and late allergic symptom response in the nose. The challenge was performed after topical pretreatment with the glucocorticosteroid budesonide (200 µg twice daily) for 14 d and with placebo in a double-blind, cross-over trial. The early response, consisting of sneezing, discharge, and blockage, was followed by a weak late response, consisting of a few sneezes and nose-blowings, and of a sustained nasal blockage. These symptoms did not have a well-defined peak in time, and a biphasic symptom curve could not be identified. The rechallenge response showed increased nasal responsiveness. The degree of budesonide effect on the early response varied, depending on the symptom; there was a marked effect on sneezing (72% reduction; $P < 0.01$), a moderate effect on discharge (37% reduction; $P < 0.01$), and a slight effect on blockage (17% reduction of nasal inspiratory peak flow rate; $P < 0.02$). The degree of inhibition of the rechallenge response was similar to the effect on the initial early response. The effect on the late response was very pronounced for all symptoms and signs (97% reduction of sneezes, 76% reduction of nose-blowings, 96% reduction of blockage; $P < 0.01$). In conclusion, we found it difficult in the individual subject to identify a well-defined late symptom response by criteria similar to those employed to characterize the late response in the bronchi. The effect of budesonide was more marked on sneezing than on blockage, and the drug was considerably more effective on the late response than on the early response.

H. Grønborg¹, H. Bisgaard¹,
F. Rømeling¹, N. Mygind²

¹Otopathological Laboratory, Department of Otorhinolaryngology and the ²Allergy Clinic, Department of Internal Medicine TTA, Rigshospitalet, Copenhagen, Denmark

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Niels Mygind, MD
Otopathological Laboratory
Department of Otorhinolaryngology,
Rigshospitalet
Blegdamsvej 9
DK-2100 Copenhagen
Denmark

Since the first allergen challenge of the airways was carried out by Blackley in 1873 (5), it has been obvious that there is an immediate symptom response or early response (ER). In the bronchi, the ER fades out after a few hours and is often followed by a late response (LR), which is characterized by reappearance of symptoms after 4–8 h. The airway resistance follows a biphasic curve, and the second part of this dual response is often more severe than the first part (6, 7). There is accumulating evidence that the bronchial LR is associated with inflammation and hyperresponsiveness, and it is considered to represent more closely the nature of the ongoing allergic disease than does the ER (6, 7).

There is a number of papers on late occurring increases of nasal blockage and nasal airway resistance (NAR) after allergen challenge. The reported incidence of a late blockage response has varied

considerably from 4% to 60% (8, 19, 22, 25–28, 29). These studies, however, are somewhat difficult to interpret because the criteria used for a positive LR are often vaguely defined and vary from study to study. The studies report only positive LRs in single individuals, and do not provide data from all patients tested. In addition, the considerable spontaneous variation of NAR, which occurs over a 10-h period (13), may account for some of the nasal LRs reported in individual patients.

Richardson et al. (23) and Vilsvik et al. (31) have presented mean group data for NAR, finding it to be increased by 33% at 6 h and by 40% at 7 h, respectively. These data show that a late blockage response to allergen challenge does exist in the nose, but it is not clear whether it is part of a biphasic dual response, or whether it is a sustained response in continuation with the ER.

More recently, Naclerio and coworkers (11, 14, 15) have studied the LR in the nose in detail, noting the number of sneezes 3–11 h after allergen challenge. When the allergen challenge was repeated after this period, the rechallenge response (RCR) showed increased responsiveness to allergen. NAR could not be measured with this study protocol, which necessitates the use of a vasoconstrictor spray.

In the present study, we wanted further to characterize the symptom response to allergen challenge in the nose, especially the LR, by recording sneezes, nose-blowings, and NAR/nasal inspiratory peak flow rate (N-IPFR) over a 10-h period. We wanted also to study the effect of pretreatment with the topical glucocorticosteroid, budesonide, on the full symptom response to allergen.

Material and methods

Design of the study

In a double-blind, cross-over study, grass-pollen-sensitive volunteers were treated with budesonide, as a nasal spray, and with placebo, in a randomized order for 2 weeks before allergen provocation. Nasal symptoms and signs were recorded during a 10-h period after the challenge (day 1), which was repeated on the next day (day 2). There was a 1-month washout period between the two treatment periods. The protocol was approved by the Ethical Committee of Copenhagen.

Volunteers

Thirty medical students, 15 men and 15 women, volunteered to take part in the study. Their mean age was 24.8 years (range, 18–30 years). All volunteers had hay fever symptoms in June and July and a positive skin prick test to timothy pollen. The study was undertaken outside the pollen season. None suffered from asthma or perennial rhinitis, and rhinoscopy did not reveal any gross anatomic abnormalities. None had received immunotherapy.

Treatment

Budesonide was administered as an aerosol of a micronized powder from a pressurized canister (valve size 25 μ l). The active drug and placebo were supplied as coded aerosols by the manufacturer (Astra-Draco, Lund, Sweden). Budesonide was administered as two puffs of 50 μ g into each nostril morning and evening, i.e. a daily dose of 400 μ g. Treatment was given for 14 d and, in addition, the aerosol was used on the first challenge day 1 h before the allergen provocation, in the evening, and 1 h before provocation on the second challenge day.

Allergen extract

Dialyzed timothy-pollen extract was used (Aquagen SQ[®], ALK, Copenhagen), supplied as a freeze-dried stock solution (100 000 SQ U/ml). (SQ means standardized quality, referring to the high degree of biologic and immunochemical characterization of the extract). Ampules, all from the same batch, were stored at 5°C, and fresh solutions were made every second week, stored at 5°C, and kept at room temperature for 1 h before provocation.

Nasal allergen challenge

One month before the trial, all volunteers were provoked with increasing allergen doses to establish the individual threshold dose, defined as the lowest dose causing either five sneezes within 2 min or a 50% reduction of N-IPFR. Two puffs of 0.1 ml of the allergen solution were sprayed into each nostril from a metered-dose, atomized pump spray. The provocation started with a concentration of 100 SQ U/ml and increased stepwise every 10 min with increments of a factor of $10^{0.5}$ until a positive reaction appeared, or until the concentration 100 000 SQ U/ml was reached. The individual threshold dose was used for a single nasal challenge test on two consecutive days (day 1 and day 2) at the end of each treatment period. The nasal challenges were performed between 0800 and 1000.

Recording of nasal symptoms and signs

Sneezing. The volunteers counted the number of sneezes in a 15-min period after the challenge test. On day 1, sneezing was also recorded in 1-h periods for the next 10 h (45 min for the first period).

Secretion. During the first 15 min after the provocation, nasal discharge was blown into preweighed paper handkerchiefs, and the amount was calculated by weighing. On day 1, the number of handkerchiefs used (one per nose-blowing) was recorded in 1-h periods for the next 10 h (45 min for the first period).

Nasal blockage. N-IPFR was measured by a commercially available Youtlen Peak Nasal Inspiratory Flow Meter (Clement Clarke International Ltd, London), which consists of a modified Wright low-range peak flow meter, enclosed in an airtight case to which an anesthetic face mask is attached. The highest of three recordings was used.

NAR was measured by active posterior rhinomanometry. The result was expressed as v_2 , which on the flow-pressure diagram describes the angle between the abscissa and a line through 0.0, and the

intersection between the respiration curve and a circle (26).

Statistics

Nonparametric models were used throughout the study because the sample size did not permit sensitive tests of goodness of fit with regard to parametric assumptions. Within-subject comparisons were based upon the Wilcoxon matched pairs signed rank test. When comparison was extended to more than two observations (e.g. several time points), the statistical analysis was based on the area under the curve.

Results

Nasal responses to challenge without budesonide pretreatment

All nasal symptoms reached a maximum within 15 min. They were moderately severe with an average of 7.1 sneezes, 2.7 g of secretion, a 48% decrease in N-IPFR, and a 44% increase in NAR (Fig. 1).

Sneezing almost ceased within 15 min, but a few late sneezes occurred without any indication of a peak value at a certain point of time (Fig. 1). Nasal discharge also was considerably reduced after the

first 15 min, but the data (weight versus number of nose-blowings) are not directly comparable. After an initial decrease, nasal patency increased gradually over the next 1 to 3 h, remained at a subnormal level for the rest of the day, and had almost reached a normal level after 24 h (Fig. 2).

For each volunteer we obtained two time-response curves for nasal obstruction without pretreatment: one from the pretrial challenge (data not shown), and one from the placebo pretreatment. All pairs of curves were carefully analyzed by two independent observers in order to identify late exacerbations of blockage, and to study reproducibility of the response in the individual volunteer. Some volunteers exhibited recurrence of nasal obstruction, yet others had decreased nasal airway patency at the same point of time, so the mean value did not change significantly at any point of time (Fig. 1). Thus, an LR characterized by recurrence of symptoms at a well-defined point of time could not be identified. In addition, examination of the two curves for each of the volunteers did not allow us to make a distinction between late-phase responders and nonresponders. Data on sneezing and on discharge were too few to justify an analysis of the existence and reproducibility of an LR.

Early-phase sneezing, nasal discharge, and obstruction measured by the peak flow meter, but not

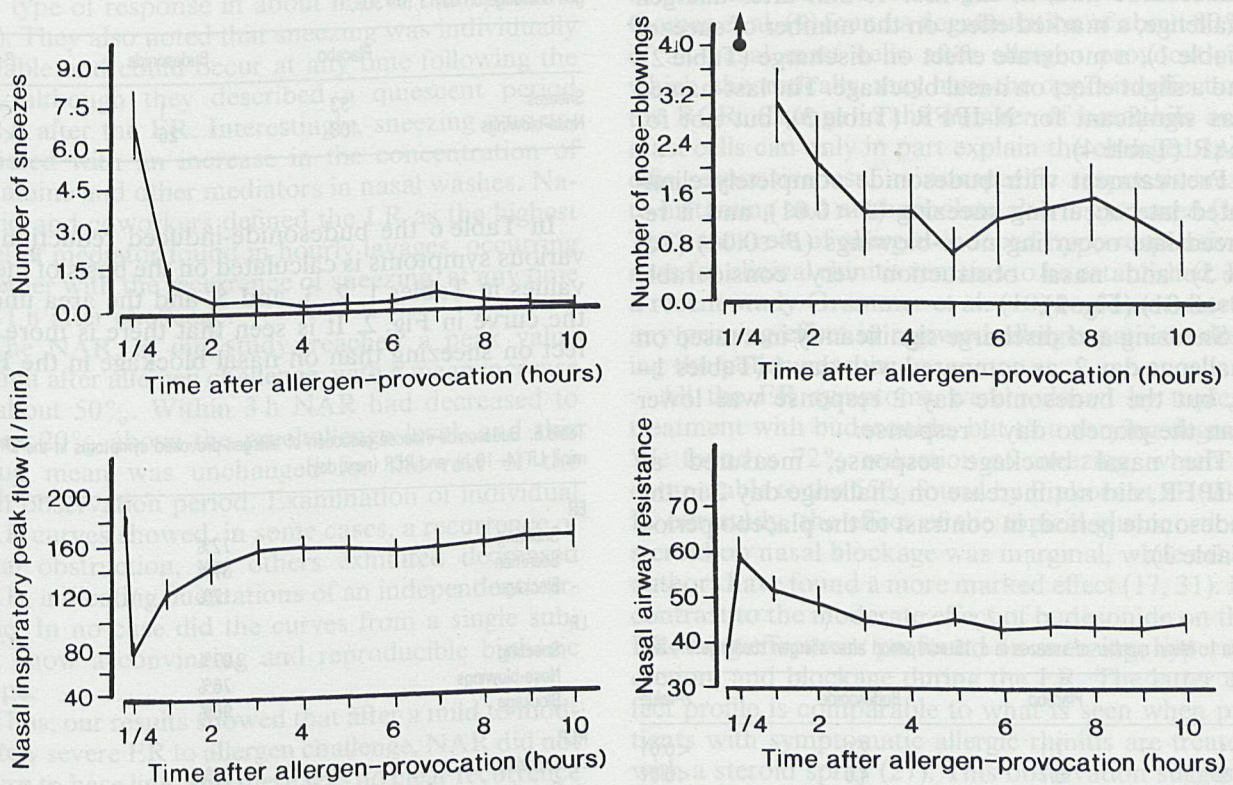


Fig. 1. Nasal symptom response to allergen challenge on day 1 in the placebo period (mean $\pm$ SEM). Note that nasal secretions collected during the first 15 min are not included.

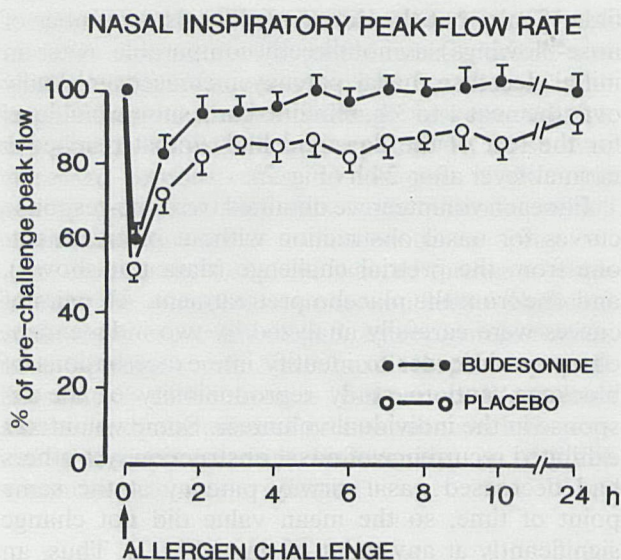


Fig. 2. Allergen-induced change in N-IPFR on day 1 in percentage of prechallenge values (mean $\pm$ SEM).

by rhinomanometry, were significantly increased on challenge day 2, as compared with day 1 (Tables 1–4).

Nasal responses to challenge with budesonide pretreatment

Budesonide had, in the first 15 min after allergen challenge, a marked effect on the number of sneezes (Table 1), a moderate effect on discharge (Table 2), and a slight effect on nasal blockage. The last-named was significant for N-IPFR (Table 3), but not for NAR (Table 4).

Pretreatment with budesonide completely eliminated late occurring sneezing ($P < 0.01$), and it reduced late occurring nose-blowings ($P < 0.01$) (Table 5) and nasal obstruction very considerably ($P < 0.01$) (Fig. 2).

Sneezing and discharge significantly increased on challenge day 2, as compared with day 1 (Tables 1–2), but the budesonide day 2 response was lower than the placebo day 1 response.

The nasal blockage response, measured as N-IPFR, did not increase on challenge day 2 in the budesonide period, in contrast to the placebo period (Table 3).

Table 1. Mean number of sneezes in a 15-min period after allergen challenge ($n=30$)

	Placebo	Budesonide	P-value
Day 1	7.1	2.0	<0.01
Day 2	10.7	4.0	<0.01
P-value	<0.01	<0.01	

Table 2. Mean amount of secretion (g) in a 15-min period after allergen challenge ($n=30$)

	Placebo	Budesonide	P-value
Day 1	2.7	1.7	<0.01
Day 2	4.1	2.1	<0.01
P-value	<0.01	<0.01	

Table 3. Mean change in N-IPFR 15 min after allergen challenge, in percentage of prechallenge values ($n=30$)

	Placebo	Budesonide	P-value
Day 1	-48	-40	<0.02
Day 2	-56	-32	<0.01
P-value	<0.02	NS	

Table 4. Mean change in NAR 15 min after allergen challenge, in percentage of prechallenge values ($n=30$)

	Placebo	Budesonide	P-value
Day 1	+44	+43	NS
Day 2	+43	+36	NS
P-value	NS	NS	

Table 5. Total number of sneezes and nose-blowings in the 4–10-h period after allergen challenge on day 1 ($n=30$)

	Placebo	Budesonide	P-value
Sneezes	33	1	<0.01
Nose-blowings	108	26	<0.01

In Table 6 the budesonide-induced reduction of various symptoms is calculated on the basis of mean values in Tables 1, 2, 3, and 5, and the area under the curve in Fig. 2. It is seen that there is more effect on sneezing than on nasal blockage in the ER,

Table 6. Budesonide-induced reduction of allergen-provoked symptoms in the ER (15 min), LR (4–10 h), and RCR (next day)

ER	
Sneezing	72%
Secretion	37%
Blockage	17%
LR	
Sneezing	97%
Nose-blowings	76%
Blockage	96%
RCR	
Sneezing	63%
Secretion	49%
Blockage	43%

and that the symptoms of the LR are almost completely ablated.

Discussion

It has previously been shown that the ER to allergen in the nose is followed by an inflammatory LR, which is characterized by an influx of basophils (2), with release of mediators (15) and an influx and activation of eosinophils (3, 4). The aim of the present study was to characterize the symptom response which may be associated with these late inflammatory events.

We found that the early symptom response was followed by sneezing, nose-blowings, and nasal blockage during the 10-h observation period. Compared with the ER (mean 7.1 sneezes), however, the late sneeze response was weak (mean 0.2 sneeze per hour). Late sneezing occurred evenly scattered over the entire observation period without indication of a peak in time (Fig. 1). Nasal discharge, recorded as nose-blowings, followed a similar pattern. Our results indicate that sneezes and nose-blowings, because of their low numbers, may be unreliable parameters for the documentation of an LR in the individual subject.

In 1985 Naclerio and coworkers (15) observed a late recurrence of sneezing in 9 of 12 allergen-challenged patients, and later the same authors found this type of response in about half of their patients (11). They also noted that sneezing was individually variable and could occur at any time following the ER, although they described a quiescent period 1–2 h after the ER. Interestingly, sneezing was associated with an increase in the concentration of histamine and other mediators in nasal washes. Naclerio and coworkers defined the LR as the highest level of mediator found in hourly lavages, occurring together with the recurrence of sneezing, at any time 3–11 h after challenge.

The NAR, in our study, reached a peak value 15 min after allergen challenge, with a mean increase of about 50%. Within 3 h NAR had decreased to about 20% above the prechallenge level, and this group mean was unchanged for the rest of the 10-h observation period. Examination of individual NAR curves showed, in some cases, a recurrence of nasal obstruction, yet others exhibited decreased NAR, indicating fluctuations of an independent variable. In no case did the curves from a single subject show a convincing and reproducible biphasic shape.

Thus, our results showed that after a mild to moderately severe ER to allergen challenge, NAR did not return to base line, and there was no clear recurrence of nasal blockage. Instead, there was a long-lasting partial blockage, suggesting that a slow improve-

ment of ER blockage continued in an LR without a clear distinction between the two phases.

Consequently, our results do not indicate that allergen challenge in the nose, in contrast to the bronchi, is typically characterized by a biphasic change of airway resistance and a genuine dual response. However, the study of a limited number of patients does not rule out the existence of a dual blockage response in single subjects, and it is also possible that a more vigorous allergen challenge would give a clearer late symptom response.

Our findings are apparently different from those of a number of authors who have reported recurrence of nasal blockage in 4–60% of the challenge tests (8, 19, 22, 25, 28–29). However, these studies have reported results from individual responders only, while the results from nonresponders were not presented, and it should be pointed out that these studies have not documented a return to base line of NAR or a biphasic symptom curve for group mean values. Only two papers have published mean NAR from all challenged patients, but only at one time point (23, 31); they showed significantly reduced levels at 6–7 h after challenge.

Our results agreed with those of earlier studies which have shown allergen-induced increase in mucosal reactivity at the RCR (1, 14). Recruitment of basophils during the LR, as shown by Bascom et al. (2), may be part of the explanation of this “priming” of the nasal mucosa to allergen. On the other hand, Gomez et al. (9) found a degranulation of about 80% of all nasal mast cells after allergen provocation, which, theoretically, may have the opposite effect on the RCR. Change in the number of basophils and mast cells can only in part explain the changed specific responsiveness, as nonspecific responsiveness to histamine and methacholine also is increased (1). The exact role of allergen-induced hyperresponsiveness for clinical rhinitis remains to be established. In a recent study Grammer et al. (10) could not detect any priming effect in ragweed-allergic patients during the pollen season.

All the ER symptoms were reduced by topical treatment with budesonide, but to a varying degree. We found a 72% reduction of sneezing, which is comparable to the 55% found by Pipkorn et al. (21). In our study, the effect of the topical glucocorticosteroid on nasal blockage was marginal, while other authors have found a more marked effect (17, 31). In contrast to the moderate effect of budesonide on the ER, drug effect was profound on sneezing, hypersecretion, and blockage during the LR. The latter effect profile is comparable to what is seen when patients with symptomatic allergic rhinitis are treated with a steroid spray (27). This observation suggests that the LR may be more important than the ER for the clinical expression of allergic rhinitis. But we

must be aware of the fact that models are oversimplifications of actual disease. A nasal challenge in the laboratory involving administration of high concentrations of allergen in solubilized form over a short time interval does not imitate natural exposure to low concentrations of allergen in particulate form over prolonged periods. Natural exposure consists of 15000 minute allergen challenges per day and a corresponding number of accumulated ERs, LRs, and RCRs.

There is convincing evidence that the early sneeze response is associated with degranulation of mast cells (9, 14, 21), and that histamine is by far the most important mediator of this response (12, 16). We have confirmed earlier studies showing that the ER can be reduced by pretreatment with a topical steroid. Furthermore, Pipkorn et al. (21) found that such pretreatment caused a 75% reduction of allergen-induced histamine release to nasal lavage fluid. The mode of action of this type of therapy on the ER, however, is unclear, as *in vitro* studies have shown that degranulation of human airway mast cells is not inhibited by pretreatment with glucocorticosteroids (24). Theoretically, it could be an explanation of the above findings that prolonged therapy even in asymptomatic subjects causes a depletion of mast cells, and this hypothesis gains support from the observation that prolonged therapy is able to reduce an increased number of mast cells in symptomatic rhinitis patients (18, 30). However, Pipkorn (20) did not find a reduced number of mast cells in asymptomatic pollen-allergic subjects treated with budesonide for 1 week.

While the effect of topical steroids on the ER remains unclear, the mechanisms of steroid activity on the LR is easily explained by the well-known anti-inflammatory activities of these compounds (27).

In summary, we have described the symptom response to a mild to moderately severe allergen challenge in the nose. Most symptoms occurred during the ER. There were some late occurring symptoms, consisting of occasional sneezes and nose-blowings, and a sustained nasal blockage. However, we were not able to identify a consistent, late-symptom response, characterized by recurrence of symptoms at a well-defined point of time, and being part of a dual response with a biphasic curve for airway resistance. We conclude, therefore, that the LR in the nose is less consistent and well defined than that in the bronchi. While budesonide had a moderate inhibitory effect on ER symptoms, it virtually eliminated all LR symptoms.

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