

Effect of a single dose of a topical glucocorticoid and a cyclo-oxygenase inhibitor on allergen-induced changes in nasal reactivity

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The inflammatory response of airway mucosa to allergen exposure is a complex phenomenon featuring symptoms, the influx of inflammatory cells, the release of mediators, and changes in local reactivity. These features and their pharmacological modifications can be successfully studied in nasal challenge models. We performed a nasal allergen challenge followed by a rechallenge with allergen 24 h later in order to monitor changes in specific reactivity due to the initial allergen challenge. Symptoms were monitored, as was the generation of TAME-esterase activity in nasal lavage fluids. Prior to each challenge a nasal brush specimen was taken. In a double blind, cross-over, double-dummy manner the patients were pretreated with placebo, a single dose of 200 µg of budesonide (topical corticosteroid) given 2 h prior to rechallenge with allergen or 600 mg ibuprofen (cyclo-oxygenase inhibitor) given per os t.i.d. to steady state starting 24 h prior to the initial allergen challenge. Treatment with ibuprofen induced a slightly lower composite symptom score ($P < 0.05$) at the initial allergen challenge when compared with placebo. No differences were noted in the relevant TAME-esterase activities. The allergen challenge resulted in significantly increased proportions of eosinophils in the brush specimens 24 h after the initial allergen challenge ($P < 0.001$) with no differences between the different treatment alternatives. At rechallenge there was a reduction in the symptoms of secretion and nasal blockage in both groups receiving active treatment compared with placebo ($P < 0.05$), whereas the number of sneezes was not affected and no differences were noted in TAME-esterase activity. We conclude that allergen-induced changes in reactivity appear to involve cyclo-oxygenase metabolites to some extent and that a reduction in eosinophil numbers is not a prerequisite when it comes to demonstrating an inhibition of the change in reactivity.

Key words: allergen challenge; hay fever; ibuprofen; nasal reactivity; steroids.

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Anti-inflammatory drugs, such as glucocorticoids, have become a mainstay in the clinical management of allergic inflammatory airway disease (23). On the basis of the clinical effectiveness of this treatment modality, the inflammatory component of asthma and allergic rhinitis has been stressed as the most important pathogenetic event in these diseases (23). Nasal allergen challenge models have previously been utilized in an effort to determine possible gluco-

corticoid effects on various parameters of the inflammatory response to an allergen challenge (1, 2, 5, 6, 21, 22). It has been shown that prolonged pretreatment with topical glucocorticoids inhibits the symptoms occurring at a late stage, the influx and activation of inflammatory cells, as well as the changes in specific and non-specific reactivity (1, 2, 5, 6, 21). The latter two phenomena were shown to be blocked to the same extent even if the glucocorticoid treatment

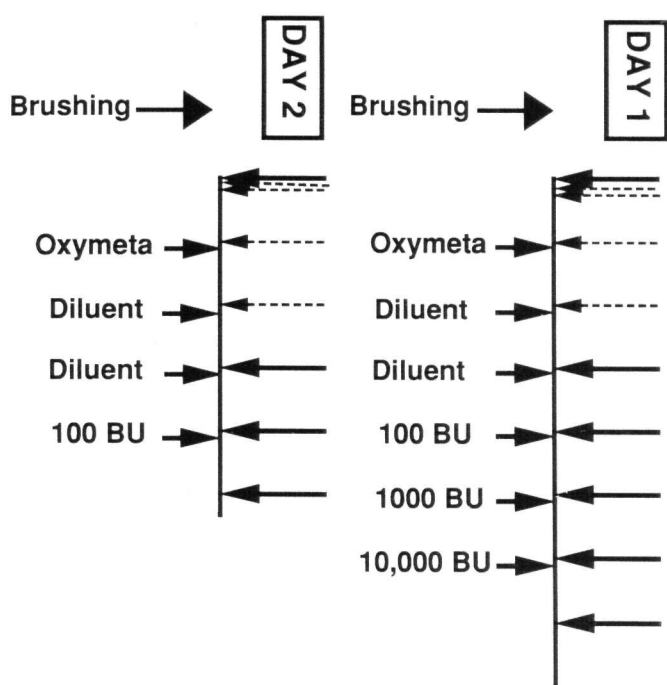


Fig. 1. Schematic outline of the challenge/lavage procedure on the 2 different days. Arrows above the line indicate lavages with 10 ml saline and arrows below the line indicate the delivery of oxymethazoline and the various challenges. Thick arrows indicate that the lavage fluid was analysed for TAME-esterase activity. Thin dashed arrows indicate that the lavage fluid was discarded. A nasal brush specimen was obtained prior to each challenge/lavage procedure as indicated by thick arrows.

was initiated just after the initial allergen challenge (1). To our knowledge no investigation has as yet been conducted to determine whether even shorter treatment times have any inhibitory effect on these two features and whether it is possible selectively to influence only one of them.

Further, it is not known whether other anti-inflammatory drugs have any inhibitory effect on the inflammatory events occurring at a late stage in the upper airways as has been suggested from animal studies (10, 11).

MATERIAL AND METHODS

Study design

A double-blind, cross-over, placebo-controlled design was used. The study was performed outside the pollen season in the study area. Active treatment or placebo was given starting either

24 h before the initial allergen challenge (ibuprofen) or 2 h prior to rechallenge on day 2 (budesonide). Prior to each challenge a brush specimen was taken from the nasal mucosa. A nasal lavage procedure was used to monitor the response following the allergen challenges. The nasal lavage fluid was analysed for TAME-esterase activity and the symptoms of nasal secretion, blockage and sneezing were rated by the patients.

Patients

Twelve patients (8 men and 4 women; age range 18–33 years, mean 24.8) with a positive history of seasonal allergic rhinitis and a positive skin prick test to birch (*Betula verrucosa*) or timothy (*Phleum pratense*) pollen participated. All patients had previously demonstrated an increase in non-specific reactivity 24 h after an allergen challenge. They had no bronchial or dermal manifestations of their atopic disease and had all been free from any medication except for oral contraceptives for at least 3 weeks before entering the study.

Nasal challenge procedure

The challenge protocol is outlined in Fig. 1. A nasal lavage technique described in detail by Naclerio et al. (18) was used. 5 ml of isotonic saline solution was kept in each nasal cavity for 10 s while the patients kept their heads in the backward position. The lavage was then returned, immediately chilled and centrifuged at 4°C at 2000 rpm for 10 min. The sol phase was separated from the gel phase and the sol phase was aliquoted for subsequent analysis and kept at –20°C. The level of TAME-esterase (N-alpha-tosyl-L-arginine-methyl-esterase) activity in each individual lavage was analysed using a radiochemical method described by Imanari (15). The initial lavages were performed to reduce any cell free mediators present in the nose. Lavages were then performed at a fixed 10-min interval. Immediately after each lavage a challenge was performed. The challenge sequence

was 100 µg of oxymethazoline given in each nostril, 2 diluent challenges and then increasing doses of birch or timothy pollen extract. The allergen doses were 100, 1,000 and 10,000 - Biological Units (BU) which were given in an albumin diluent (Pharmalgen®, Pharmacia, Uppsala, Sweden). The lavage challenge sequence was repeated on day 2, stopping after the first allergen challenge (100 BU).

Cell sampling

Immediately prior to the initial lavage procedure on both days a brush specimen (Rhino-brush®) was obtained from the right nasal cavity as described previously (12). The obtained cell specimen was suspended in 2 ml of saline solution. 200 µl aliquots of the cell suspension were loaded on to a cytocentrifuge (Cytospin 2, Shandon Inc., Pittsburgh, PA, USA) and spun (500 rpm, 8 min) onto glass slides and left to air dry. After staining, using the May-Grünwald-Giemsa method, the total number of eosinophils per glass were counted as an expression of the total eosinophil infiltration and a differential cell count was also performed on 200 cells.

Symptom registration

Before each lavage during the entire challenge-lavage procedure the participants recorded their symptoms, using a detailed symptom score sheet. The number of sneezes were counted. The symptoms of blockage and secretion were assessed using 5-point scale ranging from 0 to 4 where 1 represented no symptoms and 4 represented intolerable symptoms immediately before each lavage. A composite symptom score was then calculated; it gave the sum of the scores of blockage, secretion and sneezing.

Investigational drugs

Using a double-blind design the patients were given either placebo or a single dose of 400 µg of budesonide (Rhinocort Aqua®, DRACO AB,

Lund, Sweden) intranasally 2 h prior to rechallenge on day 2, or 600 mg of ibuprofen (Brufen™, Boots, U.K.) t.i.d. starting 24 h prior to the initial challenge to reach steady state using a double-dummy technique. A wash-out period of 2 weeks followed each challenge-rechallenge procedure. The dose of budesonide is the recommended daily dose for the treatment of seasonal allergic rhinitis (12) and the dose of ibuprofen is well in line with the recommendations for the treatment of occasional pain (13).

Statistics

Statistical evaluations were performed on a microcomputer (Macintosh, Apple) with the aid of a statistical software package (Statview™ 512 +, BrainPower Inc., Calabasas, CA, USA). An analysis of variance was performed to evaluate any differences between given treatments (active or placebo), the influx of eosinophils, TAME-esterase activity and clinical symptoms. If a statistical significance emerged, a Student's t-test for paired data was used for further analysis. *P*-values of < 0.05 were considered significant (two-sided alternative).

RESULTS

Nasal clinical response

All the patients completed the study and no adverse reactions were seen. Not surprisingly, increasing the dose of allergen on day 1 caused increased nasal symptoms (Fig. 2). These symptoms, expressed as a composite clinical symptom score, were significantly ($P < 0.05$) reduced by pretreatment with ibuprofen when compared with placebo.

After treatment with placebo, rechallenge on day 2 caused a significantly increased nasal response in the individual symptoms of both secretion and nasal blockage to the same amount of allergen (100 BU) (Table 1). Both active treatments significantly ($P < 0.05$) reduced these symptoms when compared with the placebo administration. The mean number of

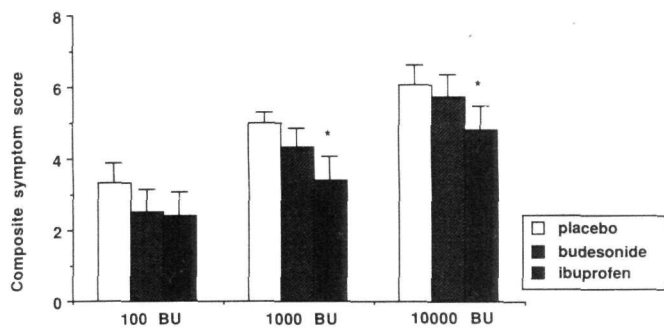


Fig.2. Composite nasal symptom score 10 min after the 3 allergen challenges on day 1. Increasing doses of allergen caused increased nasal symptoms. These symptoms were significantly reduced by pretreatment with ibuprofen compared with placebo. **P* < 0.05 active treatment vs. placebo.

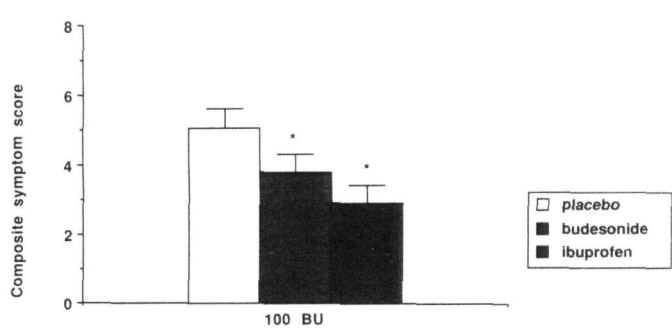


Fig.3. Composite nasal symptom score 10 min after the allergen rechallenge on day 2, i.e. 24 h after the initial allergen challenge. Active treatment significantly reduced symptoms. **P* < 0.05 active treatment vs placebo.

sneezes in the placebo group increased from day 1 to day 2, but this increase was not statistically significant (Table 1). The number of sneezes was not significantly affected by any treatment when compared with placebo.

When the symptoms were expressed as a composite symptom score the rechallenge on day 2 induced a significantly higher value after challenge with the same dose of allergen. In the placebo group this value increased from 1.9±0.3 to 3.1±0.3 (*P* < 0.05). This increase was significantly reduced (*P* < 0.05) by both active treatment alternatives as shown in Fig. 3.

Cell samplings

A significant influx of eosinophils was noted 24 h after the initial allergen challenge regardless of treatment (Table 2). The proportion of eosino-

phils increased from 0.6±0.3 to 13.1%±4.0 (*P* < 0.001) during treatment with placebo. This increase occurred to a similar degree regardless of treatment.

TAME-esterase activity

The levels of TAME-esterase in the nasal lavage fluid did not change significantly from day 1 to day 2 nor was any difference seen between the treatment alternatives. A small, but not significant, increase was seen from day 1 to day 2. In the placebo group it increased from 23,646±5,956 cpm after the initial challenge with 100 BU to 30,689±6,148 cpm on day 2 after rechallenge (Fig. 4).

DISCUSSION

The present study confirms previous observations that nasal symptoms following allergen

Table 1.
Mean symptom score (±SEM) for individual symptoms obtained after challenge with 100 BU day 1 and at rechallenge at day 2

Symptoms	Secretion		Blockage		Sneezing	
	day 1	day 2	day 1	day 2	day 1	day 2
Placebo	1.3±0.3	1.8±0.3*	0.3±0.1	1.3±0.3*	5.5±1.7	7.8±2.3
Budesonide	1.2±0.3	1.3±0.3*	0.3±0.2	0.7±0.2*	5.6±1.9	5.8±1.4
Ibuprofen	0.8±0.2	1.0±0.3*	0.1±0.2	0.6±0.2*	4.3±1.8	4.7±1.2

+ statistically significant difference (*P* < 0.05) versus day 1.
* statistically significant difference (*P* < 0.05) versus placebo treatment.

challenge increase at a rechallenge performed 24 h after the initial challenge. This increase was abolished by topical glucocorticoid treatment, even if the glucocorticoid was given as a single dose only 2 h prior to rechallenge, and it was also blocked by pretreatment with ibuprofen. The latter treatment also reduced the symptoms in the immediate reaction following the initial allergen challenge.

The subjects in the present study were selected from those who had already demonstrated the presence of an increase in non-specific reactivity 24 h after an allergen challenge before entering the study. The entry criteria were based on the presence of a change in non-specific reactivity, which is a relatively easy parameter to monitor, while in the present study we chose to study changes in specific reactivity in order to relate the present findings to a previous study using other pretreatment times (1). It was, nevertheless, considered relevant since it has been previously demonstrated that there is a high degree of correlation between the changes in specific and non-specific reactivity after a nasal allergen challenge (2).

In the present study we chose to measure the changes in the levels of TAME-esterase activity in the lavage as a marker of the inflammatory response to the allergen. This was based on previous findings by Naclerio et al. (18) that this marker best reflected the symptoms obtained in a nasal allergen procedure. It has also been shown to be a useful marker in the objective monitoring of hay fever patients during natural allergen exposure (4). This may be because the TAME-esterase activity not only reflects the activation of a single mediator cell but also takes account of additional contribu-

tions from cellular, glandular and vascular origins (7). This may also explain why minor changes in only some of the nasal symptoms can not be detected using this marker, as was evident in the present study where the minor inhibition of symptoms by ibuprofen during the immediate response as well as the inhibitory effect on the change in reactivity was not reflected by a reduction in TAME-esterase activity.

It is interesting to note that the single dose of topical glucocorticoid given only 2 h prior to the rechallenge was able to block the change in reactivity. It was thus possible to demonstrate this inhibitory effect of the glucocorticoid on the change in reactivity, although we allowed any late phase response to fully develop before the glucocorticoid was given. Further, this glucocorticoid effect could be separated from any inhibitory effect on local eosinophil numbers. Previ-

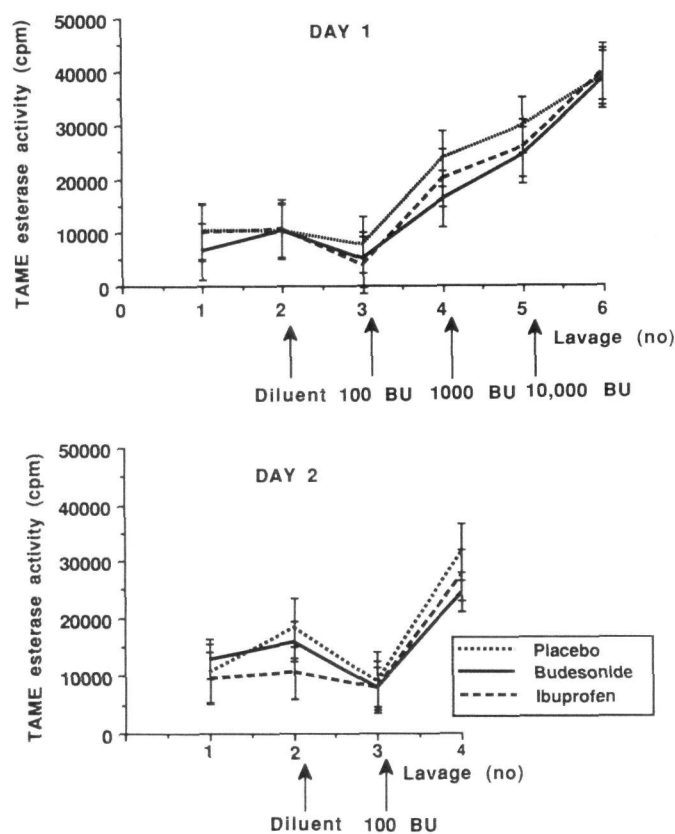


Fig. 4. A) Levels of TAME-esterase activity in nasal lavage fluid on day 1. Challenge with increasing doses of allergen caused increasing levels of TAME-esterase 10 min later regardless of treatment (lavages 4–6). B) Levels of TAME-esterase activity in nasal lavage fluid on day 2. Baseline values were not significantly different from day 1. Rechallenge with allergen caused a small increase in TAME-esterase. No effects of treatment were seen.

Table 2.

Proportions of eosinophils ($\pm$ SEM) in differential cell counts before initial challenge at day 1 and day 2.

Challenge day	Eosinophils (%)	
	day 1	day 2
Placebo	0.6 ± 0.3	$13.1 \pm 4.0^{***}$
Budesonide	0.8 ± 0.6	$12.3 \pm 4.4^{***}$
Ibuprofen	1.8 ± 0.9	$12.0 \pm 4.5^{***}$

*** statistically significant difference ($P < 0.001$) versus day 1

ous studies of prolonged treatment with topical glucocorticoids have demonstrated a simultaneous inhibition of several features of the nasal allergic response to allergen exposure during both the immediate reaction (21) and events occurring at a later stage, such as symptoms, the influx and activation of eosinophils (6, 21, 22), and changes in reactivity (21, 22). Using the initiation of treatment as a variable it was thus possible to influence one of these subsequent events without any inhibitory effect on the other. Although challenge experiments in the skin have previously shown that the initial eosinophil infiltration can be blocked after 2 h of glucocorticoid treatment (14), it might well be that this is only valid if the glucocorticoid is present during the phase of active chemotactic signalling, or during the actual passage of the cells from the vasculature. Only a minimal effect on eosinophil numbers might then be seen when the eosinophils are outside the vascular bed. Although we were unable to influence the number of eosinophils, we might well have influenced their state of activation thus contributing to the change in reactivity. However, this appears to be less likely since no causal relationship between these two phenomena has been established. From the present study it is not possible to establish the exact nature of the inhibitory effect on the change in reactivity. Although there are several possibilities, it appears less likely that the effect is related to a change in cell number but rather to a cell function due to the well-known lag phase in the effect of glucocorticoids (23). We can only speculate that this inhibitory effect might be due to an effect on the barrier function of the epithelial lining since this may well play a crucial part in the development of the change in reactivity.

The other anti-inflammatory drug used in the present study appeared to produce interesting effects. It is not known whether these effects are linked to a reduction in the release of prostaglandins like that produced by the non-steroidal, anti-inflammatory drugs (NSAID) (28). Drugs such as acetylsalicylic acid, indomethacin and ibuprofen are all potent inhibitors of the cyclo-oxygenase pathway of the metabolism of arachidonic acid (24, 27, 28). The use of these

compounds in allergic patients is, however, restricted due to the well-known adverse effects including anaphylaxis (25) which has been suggested is partially due to a shunting effect towards the lipooxygenase pathway (26). In the upper airways, cyclo-oxygenase metabolites such as PGE, PGD_2 , $\text{PGF}_{2-\alpha}$, 6-keto- $\text{PGF}_{1-\alpha}$ and thromboxane are released during the early allergic reaction of the nasal mucosa. No shunting by acetylsalicylic acid towards the lipooxygenase pathway was found in a previous nasal allergen challenge study (9). The minor inhibitory effect of ibuprofen in the present study appears to be in accordance with a previous study where it was shown that the addition of a cyclo-oxygenase inhibitor to antihistamine treatment results in a transient reduction in symptomatology in hay fever patients compared with those treated with antihistamine alone (8). The induction of a reduced change in reactivity appears to validate some recent findings in the lower airways where it was reported that treatment with indomethacin inhibited the development of bronchial hyperresponsiveness (16) with a maximum effect on days 3–5 after the start of the treatment. Our findings thus appear to indicate that cyclo-oxygenase metabolites seem to be involved in the development of allergen-induced reactivity. However, such a statement would only hold true if the change in reactivity is independent of the minor reduction in the symptoms of the initial allergen challenge. Since the changes in reactivity in previous studies did not correlate to the immediate nasal allergic reaction (18) such an assumption may well be valid. An alternative less likely explanation could be that leukotrienes, which are the product of arachidonic acid metabolism along the lipooxygenase pathway, may increase due to the cyclo-oxygenase pathway inhibition and have a factual protective role, but such an hypothesis is not supported by experimental data. In this context it should be noted that in studies of the dog (10, 11) one particular cyclo-oxygenase metabolite, thromboxane, has been suggested as an important mediator of the development of changes in local mucosal reactivity.

In summary, we conclude that allergen-induced changes in nasal reactivity appear to in-

volve cyclo-oxygenase metabolites. The changes are noted without any evidence of a reduction in eosinophil influx. A similar reduction in nasal reactivity was also seen after single treatments with topical steroids given 2 h prior to rechallenge.

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