

Glucocorticoid-induced attenuation of mucosal exudation of fibrinogen and bradykinins in seasonal allergic rhinitis

Svensson C, Klementsson H, Andersson M, Pipkorn U, Alkner U, Persson CGA. Glucocorticoid-induced attenuation of mucosal exudation of fibrinogen and bradykinins in seasonal allergic rhinitis. *Allergy* 1994; 49: 177–183. © Munksgaard 1994.

The mucosal plasma exudate with its proteins, enzymes, derived peptides, and matrix molecules is an important factor in inflammatory airway diseases. This study investigated whether topical glucocorticosteroid treatment influences mucosal exudation of bulk plasma (fibrinogen) and the generation of plasma-derived mediators (bradykinins) in seasonal allergic rhinitis. Twenty-two patients with birch-pollen-induced allergic rhinitis participated in a double-blind, randomized, placebo-controlled study during the birch pollen season in 1989. After a 2-week run-in period, the participants received treatment with budesonide (200 µg per nasal cavity and day) or placebo. The patients kept a diary to record their daily nasal symptoms (itching, sneezing, nasal blockage, and secretion). The amount of birch pollen in the air was determined with the aid of a Burkhard pollen trap. A nasal lavage was performed once a week, and the levels of bradykinins and fibrinogen were determined in the lavage fluid samples. The birch pollen season was very mild, resulting in only minor nasal symptoms. In spite of the low pollen exposure, treatment with budesonide reduced the lavage fluid levels of both bradykinins and fibrinogen. The present results show that topical glucocorticosteroid treatment attenuates plasma exudation and the generation of plasma-derived mediators in seasonal allergic rhinitis. This action may not result from simple vascular antipermeability effects of the drug but may rather reflect the anti-inflammatory efficacy of topical glucocorticoids in the airway mucosa.

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Key words: allergic rhinitis; bradykinins; fibrinogen; plasma exudation; topical glucocorticoids.

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Accepted for publication 27 May 1993

Airway luminal entry of plasma in response to mucosal challenges has been proposed as a specific sign of the ongoing inflammatory process in the airway mucosa and lamina propria (21, 22). The mucosal exudation process may primarily be regarded as a defense mechanism in the airways (23), but may for several reasons also be pathogenetic in chronic airway inflammation (19, 20). Exudation of plasma into the human airway lumen and the concomitant generation of plasma-derived mediators have been demonstrated after nasal histamine challenges of normal persons (35), after allergen challenges of patients with allergic rhinitis (7, 27) and allergic asthma (31), and in seasonal allergic rhinitis (34).

Glucocorticosteroids are potent anti-inflam-

matory agents with a variety of actions. From animal airway experiments we know that glucocorticoids have a capability to attenuate inflammatory stimulus-induced mucosal exudation of plasma (10). Topical glucocorticoids reduce the release of mediators during the immediate and late response after allergen challenge of the upper airways (28). Furthermore, glucocorticoids are an effective treatment of inflammatory airway diseases including allergic rhinitis (16, 29), asthma (13, 38), perennial rhinitis (14), and nasal polyposis (17, 18, 32). The beneficial effects of topical glucocorticosteroid treatment in these diseases may partly be due to its antiexudative capability, and results suggestive of such an effect have been reported in inflammatory disorders of both the upper and lower airways (15, 20, 21, 25, 27, 39). The antiexudative action of glucocorticoids in human

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airways seems to reflect the anti-inflammatory effects of these drugs rather than simple vascular antipermeability effects (36).

The antiexudative capability of topical glucocorticoids has hitherto not been addressed in a study of seasonal allergic airway inflammation. The aim of the present study was to extend the findings from previous animal and laboratory experiments and to determine whether a topical glucocorticoid given during the Swedish birch pollen season may attenuate plasma exudation and kinin generation in the upper airways of subjects with seasonal allergic rhinitis.

Material and methods

Study design

In a double-blind, randomized, placebo-controlled study, 22 patients with allergic rhinitis caused by birch pollen were given topical treatment with a glucocorticosteroid (budesonide) during the Swedish birch pollen season of 1989. After a 2-week run-in period, the patients received treatment with topical budesonide (200 µg once daily in each nasal cavity; $n = 11$) or placebo ($n = 11$) for a total of 5 weeks. A nasal lavage was performed once a week and the lavage fluid levels of plasma exudative markers were determined.

Patients

The patients consisted of 13 men and nine women between the ages of 18 and 32 years (mean age, 24.2 years). All patients had a history of birch-pollen-induced rhinitis, a positive skin prick test for birch pollen extract (*Betula verrucosa*), and a positive reaction to nasal challenge with birch pollen. The characterization of the patients in the placebo-treated ($n = 11$) and budesonide-treated ($n = 11$) groups, respectively, was as follows: mean age 23 years (18–26 years) and 25 years (20–32 years); male/female = 7/4 and 8/3; mean duration of allergic rhinitis 12 years (6–16) and 13 years (3–25 years). Three months before the start of the present study, all patients showed allergen-induced nasal secretory hyperreactivity; i.e., enhanced nasal reactivity to methacholine challenge (6 mg) (measured as the volume of nasal surface liquid collected with an external funnel within 10 min of methacholine provocation) 24 h after nasal allergen challenge (10 000 BU of birch pollen; Pharmalgen®, Pharmacia, Uppsala, Sweden). The patients had no bronchial or dermal manifestation of their allergic disease. Rhinoscopy was performed immediately before the study and no signs of infection, polyps, or structural abnormalities were noted. Systemic or topical corticosteroid treatment was not allowed for 2 months and 1 month, respectively,

before enrollment. Before entering the study, all participants gave their informed consent and the study was approved by the ethics committee of the University of Lund, Sweden.

Investigational drug

The participants were given topical treatment daily with budesonide 200 µg per nostril (in the morning) or placebo. Budesonide and placebo (lactose) were administered as dry-powder preparations with a sniff-activated inhaler (Rhinocort Turbuhaler®, AB Astra Draco, Lund, Sweden). Terfenadine, 60 mg orally maximum twice a day, was used as escape medication for severe symptoms of allergic rhinitis. No other drugs, except for contraceptives, were allowed during the study period.

Nasal lavage procedure

Nasal lavages were performed once a week at the clinic (in the afternoon between 1500 and 1800). With a pipette, 10 ml isotonic saline solution (0.9%) was divided and instilled into both nasal cavities, while the patient flexed the head gently backward (approximately 30° from the horizontal position) during closure of the soft palate. The patients maintained this position for a few seconds, and then leaned their heads forward and expelled the nasal lavage fluid into a collection vessel. The lavage fluids were almost immediately centrifuged at 2000 rpm for 10 min; the supernatants were separated, put into aliquots, and stored at -30°C until analysis.

Immediately after the nasal lavages, a cytologic brush specimen was taken from one nasal cavity, and a methacholine challenge (6 mg) was performed in the opposite nasal cavity. The results from these procedures have been reported elsewhere (12).

Assessment of symptoms

All participants received a diary to record their daily symptoms. Nasal itching, sneezing, nasal blockage, and secretion were estimated. A 4-point scale was used where 0 = no symptoms, 1 = mild, 2 = moderate, and 3 = severe symptoms. A daily composite symptom score was calculated from the individual symptoms.

Analytic assays

Bradykinins (i.e., bradykinin and lysylbradykinin) were measured with a radioimmunoassay sensitive to 3.52 pg/ml. Tyr⁸-bradykinin (Peninsula Lab, Inc, Belmont, CA, USA) was used as tracer. Iodination was performed by the chloramine-T method (11). Bradykinin (reference substance) (Bachem Fein-

chemikalien AG, Bubendorf, Switzerland), tracer, and rabbit antihuman bradykinin (Glostrup Hospital, Denmark) were mixed in polystyrene tubes and incubated for 72 h at 4°C. Separation was accomplished with dextrane-coated charcoal (Dextrane T70, Pharmacia Diagnostica Norden AB, Uppsala, Sweden). The assay was evaluated in a gamma counter (Clinigamma, Pharmacia Diagnostica Norden AB, Uppsala, Sweden) and RIA CALC (Pharmacia Diagnostica Norden AB). The intra- and interassay coefficients of variation were 7% and 12%, respectively.

Fibrinogen was measured with a radioimmunoassay sensitive to 2 ng/ml. Iodination was made by the lactoperoxidase method (37). Rabbit antihuman fibrinogen (UCB, Brussels, Belgium) and human fibrinogen (reference substance) (Sigma, St Louis, MO, USA, and Calbiochem, San Diego, CA, USA) were used. The samples were treated in an ultrasonic bath for 15 min and centrifuged at 4500 rpm for 10 min. Standards and samples, respectively, were mixed with tracer and antiserum in polystyrene tubes and incubated for 48 h at room temperature. Separation was accomplished by adding diluted normal rabbit serum and goat antirabbit IgG (Draco AB, Lund, Sweden). The bound fraction was measured in a gamma counter (Clinigamma, Pharmacia Diagnostica Norden AB, Uppsala, Sweden), and the results were calculated with RIA CALC (Pharmacia Diagnostica Norden AB, Uppsala, Sweden). The intra- and interassay coefficients of variation were 7% and 12%, respectively.

Pollen count

The daily birch pollen counts in the air were estimated with the aid of a Burkhard pollen trap located in the area of the study. The birch pollen counts were expressed as the mean daily number of pollen grains per cubic meter of filtered air. The pollen data were kindly provided by Associate Professor Sven-Olof Strandhede, Department of Taxonomy, University of Gothenburg, Sweden.

Statistical analysis

Statistical evaluation was performed on a microcomputer (Macintosh, Apple Computers, Cupertino, CA, USA) with a software package (Staview 512+, Brainpower, Inc, Calabasas, CA, USA). A non-parametric analysis of variance for repeated observations was used to determine any significant differences between the sampling dates. If a statistically significant difference was observed, further analysis was made with the Mann-Whitney U-test and the Wilcoxon signed rank sum test. A *P* value less than 0.05 was considered to be significant.

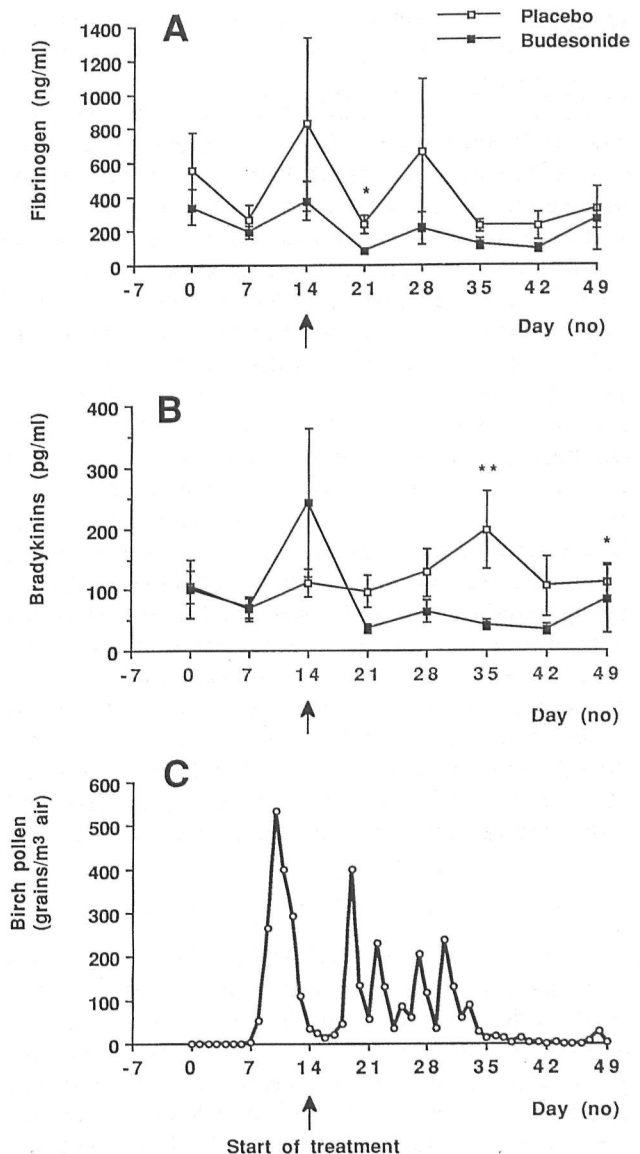


Fig. 1. Daily birch pollen counts (C, lower panel; mean daily birch pollen count per cubic meter filtered air), lavage fluid levels of bradykinins (B, middle panel; mean $\pm$ SEM), and fibrinogen (A, upper panel; mean $\pm$ SEM) during study period. Treatment was started on day 14 (arrow) separating run-in period (2 weeks) from treatment period (5 weeks). Except for moderate pollen peak during second week, pollen appearance was minor during remaining period. There appeared to be raised levels of both markers after first pollen peak (day 14; $n = 22$) and for bradykinins in placebo-treated group (day 35; $n = 11$), but neither change was statistically significantly different from levels on day 0. However, significantly decreased levels were demonstrated in budesonide-treated group ($n = 11$) during treatment period (comparison with day 14; bradykinins: $P < 0.01$ day 21 and $P < 0.05$ days 28, 35, and 42; fibrinogen: $P < 0.01$ day 21 and $P < 0.05$ days 35 and 42). While lavage fluid levels did not differ between groups during run-in period, significantly decreased levels of both bradykinins and fibrinogen were seen in budesonide-treated group during treatment (* $P < 0.05$ and ** $P < 0.01$; budesonide and placebo; $n = 11$ in each group).

Results

Pollen occurrence and nasal symptoms

The study started on 3 April and ended on 22 May (7 weeks). After a 2-week run-in period, the patients received treatment from 17 April until the end of the study (5 weeks). All participants completed the study, and data from all patients were available for analysis. The drug was well tolerated by all. The birch pollen season of 1989 in the study area was very mild. Birch pollen appeared in the air on 11 April (day 8). Except for a moderate pollen peak during the run-in period, there were only minor peaks during the remaining period (Fig. 1C). Because of the mildness of the birch pollen season, the nasal symptom scores were low, and there was no statistically significant difference in composite symptom scores between the groups (data not presented). The escape medication (i.e., single oral doses of 60 mg terfenadine) was used by four patients in the placebo-treated group (using one, two, four, and six single doses, respectively) and by two patients in the budesonide-treated group (using one and five single doses, respectively); i.e., altogether 13 and six single oral doses of terfenadine in the placebo- and budesonide-treated groups, respectively.

Lavage fluid levels of exudative indices

There were detectable levels of both bradykinins and fibrinogen in the nasal lavage fluid before the recorded appearance of birch pollen in the air (days 0 and 7) (Fig. 1). These levels did not differ between the groups during the exposure-free run-in period (days 0 and 7) or on day 14 (Mann-Whitney U-test). The mean lavage fluid levels of both markers increased after the first birch pollen peak. However, these enhancements were not statistically significant (day 0 and day 14; $n = 22$; Wilcoxon signed rank sum test) for either bradykinins or fibrinogen.

Bradykinins. During the period of treatment, the mean lavage fluid levels of bradykinins in the placebo-treated group were not different from day 14 (statistically nonsignificant differences for comparison of day 14 and days 21, 28, 35, 42 and 49; $n = 11$; Wilcoxon signed rank sum test), whereas they decreased in the group with glucocorticoid treatment (P values for comparison with day 14: $P = 0.008$ day 21; $P = 0.03$ day 28; $P = 0.03$ day 35; $P = 0.02$ day 42; and $P = 0.1$ day 49; $n = 11$; Wilcoxon signed rank sum test) (Fig. 1B). Lower mean lavage fluid levels of bradykinins were recorded in the budesonide-treated group during the entire period of treatment, and these differences between the groups reached

statistical significance on days 35 ($P = 0.002$) and 49 ($P = 0.04$) ($n = 11$ in each group; Mann-Whitney U-test) (Fig. 1B).

Fibrinogen. The lavage fluid levels of fibrinogen decreased with budesonide treatment and reached statistical significance on day 21 ($P = 0.007$), day 35 ($P = 0.02$), and day 42 ($P = 0.02$) (comparison with day 14; $n = 11$; Wilcoxon signed rank sum test), while they did not change in the placebo-treated group (differences statistically nonsignificant for comparison of day 14 with days 21, 28, 35, 42, and 49; $n = 11$; Wilcoxon signed rank sum test) (Fig. 1A). Lower mean lavage fluid levels of fibrinogen were recorded in the budesonide-treated group during the entire treatment period, and these differences between the groups were statistically significant on day 21 ($P = 0.02$) ($n = 11$ in each group; Mann-Whitney U-test (Fig. 1A).

AUC. The area under the curve (AUC) was calculated for two periods, days 0–7, representing baseline conditions (i.e., before birch pollen exposure),

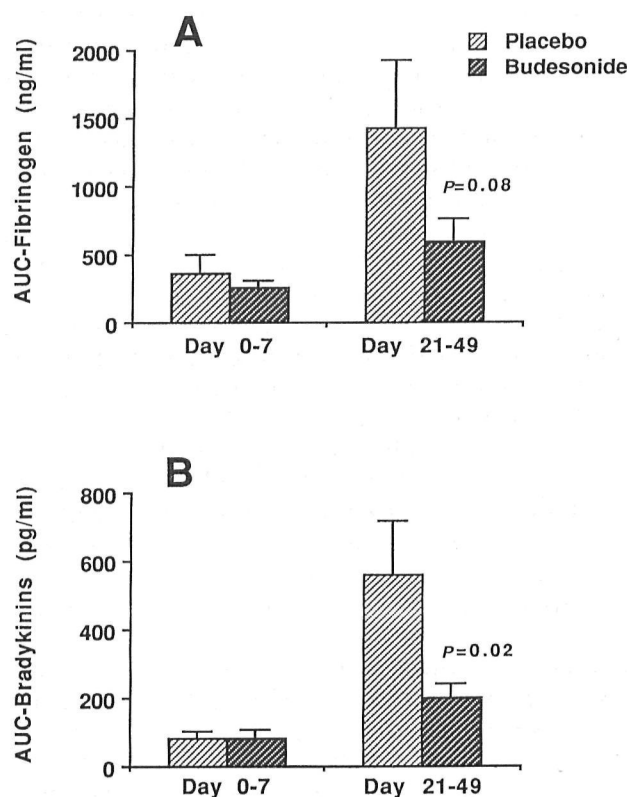


Fig. 2. Lavage fluid levels of fibrinogen (A) and bradykinins (B) expressed as area under curve (AUC) before birch pollen exposure (base-line conditions; days 0–7) and during period of treatment (days 21–49). Lavage fluid levels did not differ between groups during base-line conditions. However, during period of treatment, lower levels were recorded in budesonide-treated group ($P = 0.02$ for bradykinins and $P = 0.08$ for fibrinogen).

and days 21–49, representing the period of treatment (Fig. 2). Missing values (altogether seven values for both fibrinogen and bradykinins during both periods) were replaced by carrying the first value backward and the last value forward. During baseline conditions, no differences were shown in AUC for either fibrinogen or bradykinins, while, during treatment, lower levels were recorded; this difference reached statistical significance for bradykinins ($P=0.02$) and almost for fibrinogen ($P=0.08$) (Mann-Whitney U-test).

Discussion

In the present study of subjects with known seasonal allergic rhinitis, we observed that treatment with a topical glucocorticoid instituted during the birch pollen season produced very low nasal lavage fluid levels of fibrinogen and bradykinins. This effect was established within 1 week and lasted throughout the treatment period.

The birch pollen season of 1989 was very mild in the study area. The low-grade birch pollen exposure resulted in minor nasal symptoms without any statistically significant differences between the groups. In contrast to a previous study of seasonal allergic rhinitis from our laboratory (34), we were not able to demonstrate any statistically significant increments in the lavage fluid levels of the exudative indices during this pollen season. This could be explained by a combination of circumstances. First, the pollen exposure started with a large peak already during the run-in period, which, therefore, could not provide proper base-line levels. Secondly, since there is a known cross-reactivity (8, 9), the base-line levels might also have been influenced by hazel and alder pollen which had appeared shortly before the collection of the first lavage sample. Thirdly, the mild birch pollen season may not have consistently produced sustained inflammatory processes; hence, sustained increases in mucosal exudation of plasma would not be produced. A further confounding factor may be the circadian rhythm in exudation, peak inflammatory exudation of albumin and fibrinogen occurring in the late night and early morning (24), whereas in this study the lavage fluid was always harvested in the afternoon. Nevertheless, budesonide decreased the levels of both bradykinins and fibrinogen in the nasal lavage samples, and it cannot be excluded that the effect of this drug, particularly on the fibrinogen levels, would have been more clear-cut had the season been stronger and the fibrinogen levels greater in these patients. Whereas this action is of interest, the present study does not provide any data that may clarify the relationship between anti-exudative effects and effects on clinical symptoms of allergic rhinitis.

Bradykinins are active peptides generated from plasma kininogens by both glandular and plasma kallikrein (6, 7, 30). Thus, a contribution from glandular secretory activity to the formation of bradykinins is likely. However, the substrates for kinin generation are circulating plasma proteins (kininogens), and the provision of these precursors for further kinin generation is a result of plasma exudation (7). Hence, it is likely that the reduced levels of bradykinins are secondary to the antiexudative effect of budesonide, which should reduce the appearance of all plasma proteins in the lamina propria and the mucosa.

Fibrinogen is a large plasma protein (340 kDa). The appearance of this protein in nasal lavage fluid samples from allergic patients during seasonal pollen exposure has now been demonstrated for the first time. We have previously reported increased and dose-dependent lavage fluid levels of both albumin and fibrinogen after nasal allergen challenge (2) and particular increases in fibrinogen levels in bronchial lavage after bronchial allergen challenge (31). In agreement with the findings from these challenge experiments, the occurrence of fibrinogen in the present study would reflect extravasation and mucosal exudation of unsieved plasma. There are reasons to believe that the extravasation of fibrinogen was underestimated by this study. Fibrinogen is a reactive protein susceptible to cleavage by fibrin after contact activation. Thus, fibrinogen-consuming fibrin formation might have taken place during the exudative process (in the subepithelial tissue and on the nasal mucosal surface). In view of the possibility of fibrinogen degradation and also the enzyme dependence in bradykinin formation, it is not surprising that the lavage fluid levels of these two exudative markers did not exhibit perfect correlation.

Mucosal exudation of plasma is a characteristic feature of allergic inflammatory airway diseases and a dual function of this feature, both protective and pathogenetic, has been proposed (19, 20, 22, 23). Furthermore, it is argued that the plasma exudation response of the readily accessible human nasal mucosa well reflects the response that would occur in the relatively less accessible bronchial mucosa (26). Mucosal exudation of plasma may in several ways be involved in the pathogenesis of chronic airway inflammatory diseases. Long-lasting exudation of plasma may lead to vicious circles including activation of various plasma protein systems (e.g., kinin, complement, and coagulation systems), potentially causing aggravation and perpetuation of the inflammation. The demonstrated antiexudative effect of topical glucocorticoids is therefore to be interpreted as a desirable anti-inflammatory action. Glucocorticoids may act on several levels of the inflammatory reaction to achieve the end result of an antiexudative

effect. The possibility of a direct action on the microvascular wall has been demonstrated in animal experiments (10, 33). However, we have not been able to show such a direct vascular (endothelial) effect of topical steroids in human nasal airways (36). Glucocorticosteroids have a range of anti-inflammatory actions which may be expressed as decreased plasma exudation (25). Many of the cellular changes that may fuel airway inflammation are susceptible to topical glucocorticoids, e.g., influx and activation of eosinophils, basophils, and mast cells (1, 3, 4, 5, 12, 28). We therefore suggest that the present demonstration of glucocorticoid-induced attenuation of mucosal plasma exudation reflects anti-inflammatory cellular effects of these drugs. A lack of direct vascular antipermeability effects means that a plasma exudation defense response can readily be evoked also in glucocorticoid-treated airways.

In summary, our study demonstrates that topical glucocorticoids may prevent airway exudation of bulk plasma and the appearance of plasma-derived mediators in mild seasonal allergic rhinitis. We suggest that an antiexudative action may be an important aspect of the therapeutic actions of topical glucocorticoids in airway diseases.

Acknowledgments

This study was supported by grants from the Swedish Medical Research Council (project 8308), the Medical Faculty of the University of Lund, the Torsten and Ragnar Söderberg Foundation, the Swedish Association against Asthma and Allergy, and Astra Draco AB, Lund, Sweden.

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