

Efficacy of acrivastine in the treatment of allergic rhinitis during natural pollen exposure: onset of action

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In a placebo-controlled, randomized, and double-blind 1-day field study, the efficacy and onset of action of capsule acrivastine 8 mg were evaluated in 42 patients suffering from allergic rhinoconjunctivitis elicited by natural grass pollen exposure. Before and for 2 h after treatment, the patients scored the severity of five rhinoconjunctivitis symptoms every 10 min on a 0–5 scale (0 = no symptoms; 5 = very severe symptoms). The number of sneezes was recorded, and every 30 min, measurements of nasal peak flow were made. Before treatment, there was no difference in median total symptom score (mTSS) between the acrivastine group (A) and the placebo group (P) (12 and 12, respectively). Time of onset was estimated by an exponential decay model to be 19 min (95% confidence interval 0–39 min). A statistically significant difference in percent reduction of mTSS between A and P was observed for the first time 46 min after treatment start (A = 22%, P = 0%, $P < 0.05$). A 50% reduction in total symptom score (TSS) was achieved within 60 min by 38% in A and 17% in P (NS), and within 80 min in 52% and 17%, respectively ($P < 0.05$). The median time for 50% reduction in TSS (MT50) was 80 min for A and > 120 min for P ($P < 0.01$). The symptom score of sneezing and number of sneezes were evaluated for periods of 30 min. The difference between A and P became statistically significant from 31–60 and 61–90 min, respectively ($P < 0.05$ and $P < 0.01$). Objective and subjective determinants in the different time intervals were well correlated. Improvement of nasal congestion was observed in A at 91–120 min, as measured by nasal peak flow.

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Acrivastine is a short-acting histamine H_1 -receptor antagonist with a low sedative potential, the efficacy of which on allergic rhinitis symptoms has been proved in many short-term (7–14 d), double-blind, placebo-controlled clinical trials (1). In healthy volunteers, mean peak plasma concentrations are obtained at 1.4 h after single-dose oral administration of a capsule. The elimination half-life of acrivastine is 1.4–2.1 h, and the mean elimination half-life of the principal metabolite is 2.3 h (1).

Acrivastine has a rapid clinical-pharmacologic onset of action of less than 30 min, as shown by studies of wheal and flare reactions to skin prick test with histamine and allergen and by histamine-induced conjunctival inflammation and bronchoconstriction (1, 8, 10, 14, 16, 17). The clinical onset of action may, however, be different from the clinical-pharmacologic onset of action.

A single placebo-controlled study of acrivastine has shown the symptom score of allergic rhinitis to be lower in the acrivastine group from 2–8 h, when, after administration of acrivastine 8 mg, patients were followed hourly for 8 h, indicating a clinical onset of action within 1–2 h (6). Further studies of the clinical onset of action of acrivastine on allergic rhinitis symptoms during natural pollen exposure are needed to establish more precisely the clinical onset of action.

Pollen counts vary considerably within and between geographic areas and during the day (11), and pollen exposure consequently varies among patients. Differences in pollen exposure may have contributed to the marginal statistical differences between acrivastine and placebo seen in some studies (1). It is possible to expose patients to equal pollen concentrations in a study design placing patients in the

same small geographic area for a fixed period of time.

The aim of this 1-day study was to evaluate the efficacy and clinical onset of action of acrivastine after oral administration to patients with rhinoconjunctivitis caused by equal exposure to natural grass pollen.

Material and methods

Patients

Forty-three patients, 23 women and 20 men, mean age 29 years (range 21–48), were included in the study. All had a positive medical history of rhinoconjunctivitis caused by grass pollen, with symptoms prevailing from May to July; a positive prick test (wheal diameter ≥ 3 mm) with *Phleum pratense* (timothy) (Soluprick® 225, ALK, Denmark); and positive specific IgE, class ≥ 2 (CAP g6, Pharmacia, Uppsala, Sweden) for *P. pratense*. Six patients had experienced periods of mild asthmatic symptoms; however, none had a PC₂₀ below 2 mg/ml after bronchial histamine dihydrochloride provocation (2), and only one patient used bronchial steroids (800 µg daily). None had a history of concurrent medical diseases, except for allergic rhinitis caused by other common aeroallergens.

The study was approved by the local ethics committee (L92052), and written informed consent was obtained from all patients before the study.

Study design

The patients were randomly assigned to receive a capsule of either acrivastine 8 mg or placebo in a double-blind, field-exposure study. The investigation was undertaken in the peak grass pollen season (5). For 10 d before the exposure (run-in period), patients recorded severity of five allergy symptoms (sneezing, rhinorrhea, nasal congestion, itchy nose or throat, and itchy eyes) by daily scores of 0–5 (0 = no symptoms, 5 = very severe symptoms), in order to verify the history of allergic rhinitis caused by grass pollen. Nasal peak flow (Mini-Wright connected to face mask, Simonsen & Weel, Denmark) was measured three times daily to ensure familiarity with the procedure.

Immunotherapy had never been instituted in the patients, and none had received systemic steroids within the previous 3 months. Ten days before the study, the patients abstained from all medication except rescue medication with acrivastine 8 mg (Semprex®, Wellcome Foundation, Denmark) (maximum three capsules daily) and antazoline-naphazoline (Antistina-Privin®, Ciba-Geigy, Switzerland) (maximum 4 eye-drops daily). Three days

before the study, the patients stopped taking acrivastine, using instead the nasal decongestant xylo-metazoline 1 mg/ml (Otrivin®, Ciba-Geigy, Switzerland) three times daily, if needed. Twenty-four hours before the study, the patients stopped any medication for rhinoconjunctivitis symptoms.

The study hayfield was one of 10000 m² in a Copenhagen suburb. The hay had not been cut since the previous autumn. The pollen concentration in the air at 1.5 m above ground level was measured hourly at the location. The amount of airborne pollen was compared with concurrent measurements at 15 m above ground level in Copenhagen city. The method is described elsewhere (5).

From 0900, upon arrival at the hayfield, symptom scores was registered every 10 min. The number of sneezes was registered for periods of 10 min throughout the study, and nasal peak flow (best of three attempts) was recorded every 30 min.

When the patient reached a total symptom score (TSS) of 10 points (40% of maximum TSS), the first capsule was administered and the exact time recorded. The patients were instructed to report when they felt relief of symptoms, or after 1 h if they felt no relief. Patients recording more than 50% reduction in TSS were allowed to leave the field. If less than 50% reduction was obtained after 1 h, another capsule was administered. Symptoms were assessed every 10 min for 2 h after capsule administration. Unblinded acrivastine 8 mg was given if the patient felt no relief 2 h after administration of the first capsule. After termination of the study period, additional antiallergic medication (prednisolone tablets, antazoline-naphazoline eye-drops) was given, if needed.

Statistics

All statistical analysis was done with SAS 6.08 for windows or StatXact Turbo 2.11. In the model of exponential decay after time lag, parameters were estimated by nonlinear least squares. The linear expansion method was employed to derive approximate confidence limits for the time lag. Survival analysis of time to 50% reduction in scores was based upon the Kaplan-Meier estimator and the exact log-rank test. Treatment groups were compared with respect to proportion of patients experiencing 50% reduction in symptom score by Fisher's exact test in 2 by 2 tables. Comparison of treatment groups at each time point or interval separately was done by exact two-sample Wilcoxon rank-sum tests (Mann-Whitney). Tests of change in peak flow relative to base line were done by exact one-sample Wilcoxon signed-rank test.

All tests were performed at a 5% significance level, and 95% confidence intervals were employed.

Results

Efficacy and onset of action of acrivastine

One patient (one P) dropped out 2 d before exposure day, and three patients were excluded during exposure because of severity of symptoms, one experiencing mild asthma symptoms, one suffering from severe rhinoconjunctivitis, and one developing periorbital edema requiring treatment with steroids. Of the remaining 39 patients (21 A and 18 P), run-in data were collected from 38 (one P missing). The differences between the acrivastine group (A) and the placebo group (P) in average TSS, number of sneezes, nasal peak flow, number of capsules taken, and eye-drop administrations per day were not statistically significantly different.

All 39 patients started treatment and were available for evaluation. Twenty-five (15 A and 10 P) evaluable patients received their first capsule within 30 min, and 35 (20 A and 15 P) had started treatment within 60 min after commencement of frequent symptom score recordings (Fig. 1).

The base-line values of median total symptom score (mTSS) were 12 and 12 for A and P, respectively. The course of mTSS relative to base line was modeled with an exponential decay process with half-lives of 79 and 911 min after A and P, respectively (Fig. 2). Time to onset of action was estimated to be 19 min (95% confidence interval 0–39 min), calculated as the time lag after dosing of acrivastine until reduction from placebo level commenced (Fig. 2). At 46 min after initial dosing, a statistically significantly different reduction in mTSS relative to base line was seen for the first time between A and P (Fig. 2).

A 50% reduction in symptom score was considered to be clinically relevant. Eight A patients (38%) had 50% reduction in TSS within 60 min after first dosing, as compared with three P patients (17%), a reduction which was not statistically different ($P > 0.05$) (Table 1 and Fig. 3). At 80 min, there was a statistically significant difference between the groups for the first time (Fig. 3), and at 120 min after first dosing, 15/21 (71%) patients in A and 4/18

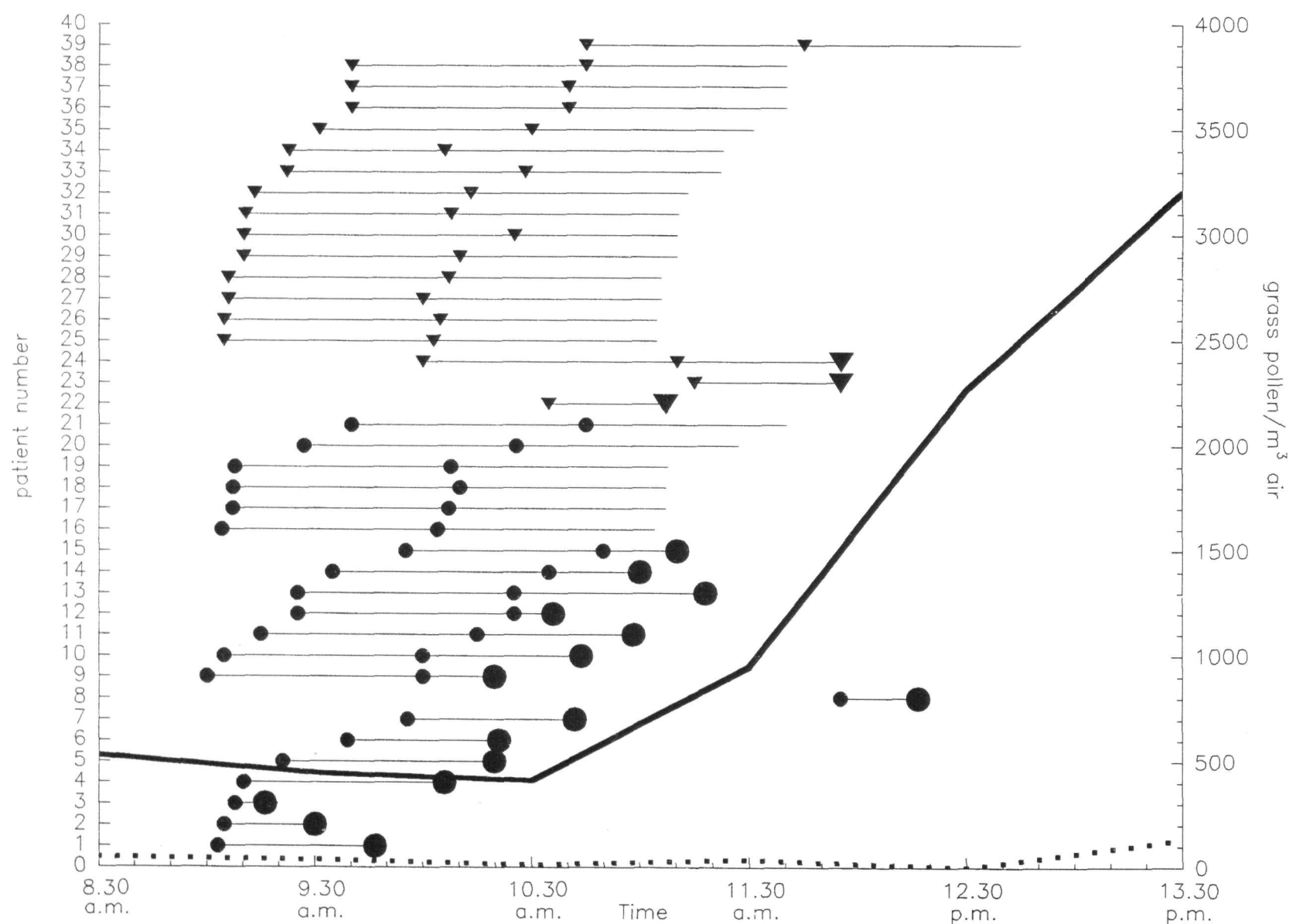


Fig. 1. Grass pollen concentration per m^3 air 1.5 m above ground level at test site (solid line) and at 15 m above ground level in Copenhagen city (dotted line) at hourly intervals. Time for capsule administration (small circles = acrivastine, small triangles = placebo) and time for 50% reduction in TSS (big circles = acrivastine, big triangles = placebo). Missing big circle or triangle at end of line indicates that 50% reduction in TSS was not achieved within 120 min.

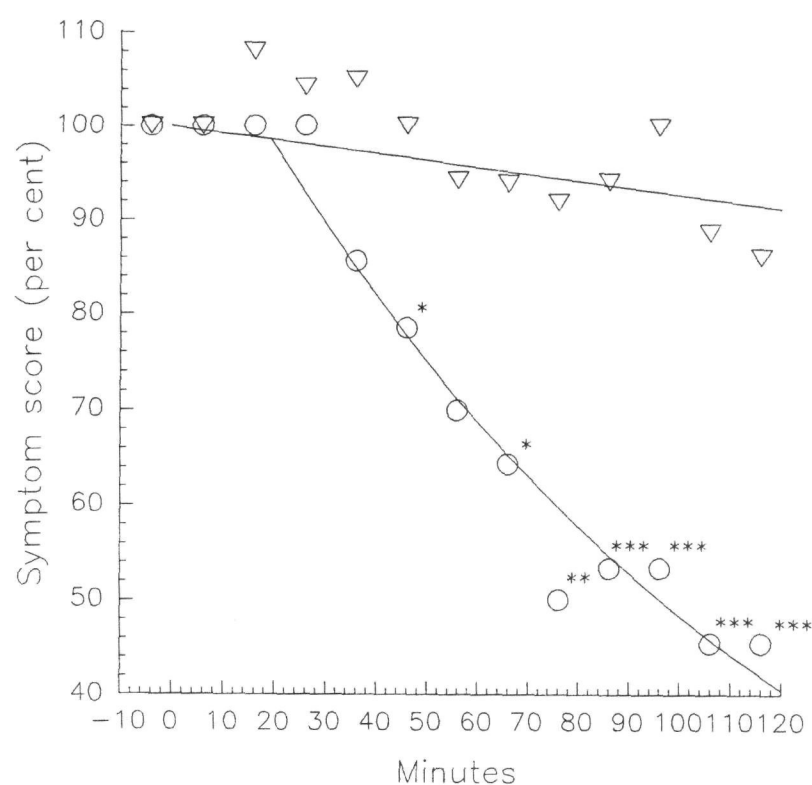


Fig. 2. Nonlinear regression of median relative TSS after first dosing. Average difference between time of first dosing and time of scoring immediately before dosing was 4 min. Symptoms were scored every 10 min, and average scoring times from dosing were therefore -4, 6, 16, ... 116 min. $\circ$ = acrivastine, ∇ = placebo. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

(22%) in P ($P < 0.01$) had reached 50% reduction in TSS. For each symptom separately, only patients with a base-line score above zero were evaluable because reduction from zero is not possible. Statistically significant differences did not occur for any single symptom at either 60 or 120 min after first dosing (Table 1).

The median time for 50% (MT_{50}) reduction in TSS for total symptoms was 80 min and > 120 min for A and P, respectively, a highly statistically significant ($P = 0.0032$) difference (Fig. 3). (The 95% confidence interval for 50% reduction in TSS ranged from 57 to 112 min in A.) No statistically significant difference in single symptoms was detected for MT_{50} .

Table 1. Number of patients with 50% reduction in symptom score within 60 and 120 min after treatment relative to patients with symptoms before treatment (A=acrivastine; P=placebo)

Symptom	≤ 60 min			≤ 120 min		
	A	P	<i>P</i> value	A	P	<i>P</i> value
Itchy eyes	8/21	5/16	0.74	16/21	7/16	0.086
Itchy nose and throat	12/20	9/17	0.75	17/20	10/17	0.14
Runny nose	7/20 ¹	5/18	0.73	13/19 ¹	9/18	0.32
Congestion	6/18 ²	1/16	0.09	9/17 ²	3/16	0.071
Sneezing	12/13	11/14	0.60	13/13	12/14	0.48
Rhinoconjunctivitis total	8/21	3/18	0.17	15/21	4/18	0.0036

¹ One patient excluded because of missing scores.

² Two patients excluded because of missing scores.

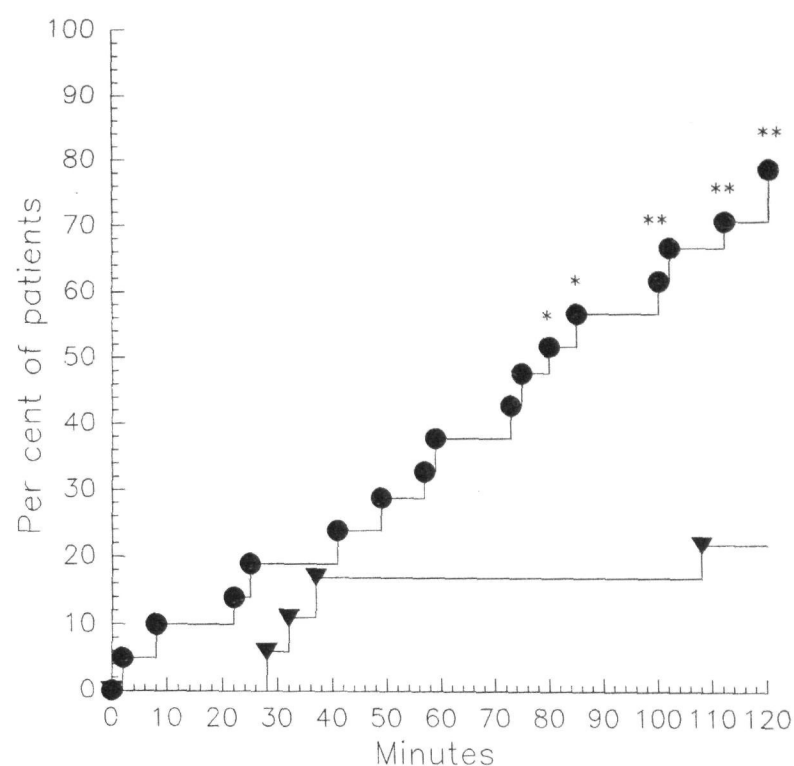


Fig. 3. Percentage of patients with 50% reduction of TSS ($n = 39$). $\bullet$ = acrivastine, $\blacktriangledown$ = placebo. * $P < 0.05$; ** $P < 0.01$.

The TSS of sneezes and the total number of sneezes in 30-min periods (3×10 min) were assessed (Fig. 4). Because few patients had a pretreatment period exceeding 30 min (Fig. 1), only periods after administration of capsules could be evaluated. There was no statistically significant difference after 30 min. The difference between A and P in symptom score and number of sneezes became statistically significant from 31 and 61 min onward, respectively ($P < 0.05$ and $P < 0.01$). The scores and numbers were closely correlated.

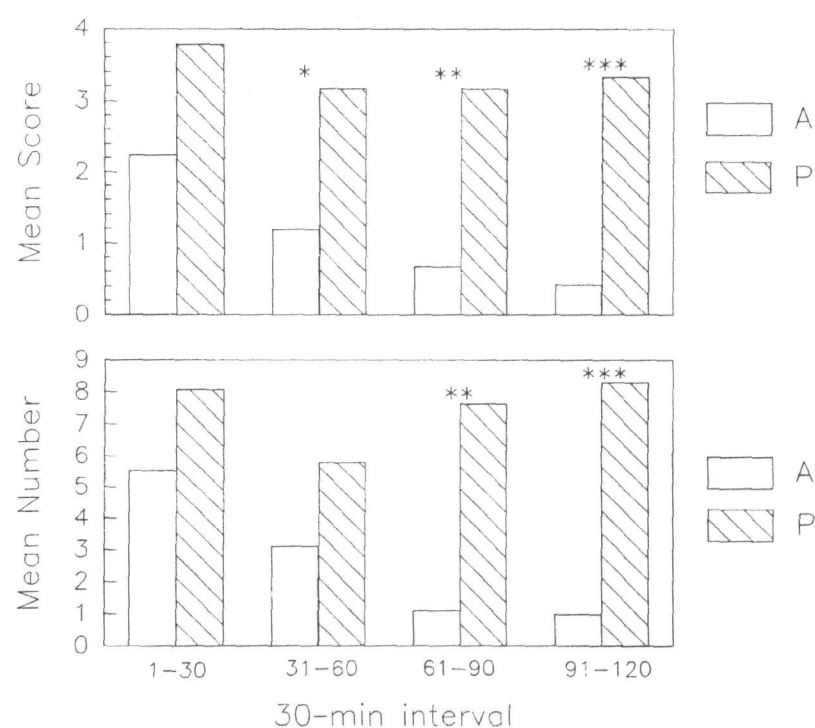


Fig. 4. Mean symptom score of sneezing and mean number of sneezes in 30-min periods. Statistically significant difference between A and P: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

Nasal peak flow was measured at 30-min intervals, thus being recorded 1–30 min after capsule administration. The mean peak flows immediately before ingestion of the first capsule were 165 and 148 l/min for A and P, respectively. The relative change from base line became statistically significantly different for A and P during the 91–120-min interval ($P < 0.01$) (Fig. 5). Relative nasal peak flow increased in A, statistically significantly different for 91–120 min ($P < 0.05$), whereas it decreased in P, but statistically significantly ($P < 0.05$) for only 1–30 min (Fig. 5).

Pollen exposure

The weather had been dry and sunny for the month preceding the study day, and some of the grasses were beyond flowering. On the day of exposure, the weather was dry and sunny with a soft breeze, and five different types of grass were flowering at the location (*Lolium perenne*, *P. pratense*, *Poa trivialis*, *Festuca pratensis*, and *Festuca rubra*). Pollen counts at 1.5 and 15 m above ground level showed a pollen ratio ground:roof of 11 at the beginning of the study and 26 at the end, verifying a heavy grass pollen exposure (Fig. 1). The local pollen concentration was less than 85 grass pollen/m³ air before 0830, rose from 0830 to 1130, and rose again from 1130 to 1330 (Fig. 1) (pollen data from before 0830 not shown).

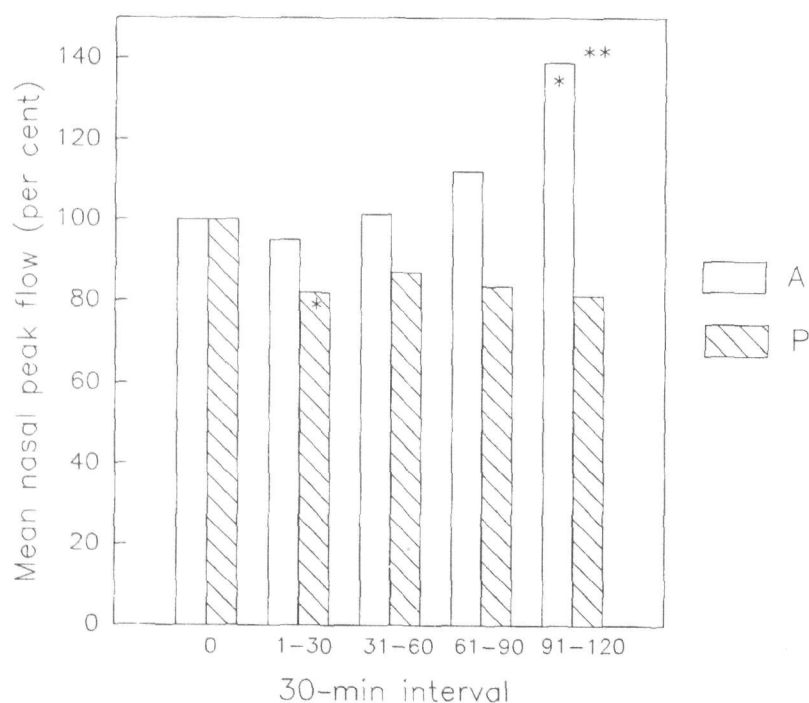


Fig. 5. Mean nasal peak flow relative to base line at 1–30, 31–60, 61–90, and 91–120 min after treatment. Statistically significant reduction from base line in P at 1–31 min. Statistically significant increase from base line in A at 91–120 min; * $P < 0.05$. Statistically significant difference between A and P at 91–120 min; ** $P < 0.01$.

Discussion

Several short-term (7–14 d), placebo-controlled studies have detected an effect of acrivastine on seasonal allergic rhinitis (1). The present study confirmed that acrivastine is efficacious in reducing allergic rhinitis symptoms, as compared with placebo. Gervais et al. (3) have shown terfenadine and acrivastine to be equally potent, and many studies comparing terfenadine and various H₁-antagonists have shown identical effectiveness in reducing allergic rhinitis symptoms, indicating that acrivastine is comparable with other second-generation H₁-antagonists.

The clinical-pharmacologic onset of action has been investigated in many comparative studies. Comparison of the onset of H₁-antagonistic action of acrivastine and terfenadine by histamine bronchial challenge has shown acrivastine to be faster acting (13). Comparative studies of inhibition of histamine-induced wheal and flare by different H₁-antagonists have found an effect of ceterizine at 40 min and of astemizole, terfenadine, and loratadine at ≥ 1 h, whereas acrivastine has shown significant inhibition after 15–25 min (1, 10), once again indicating a faster onset of action than other second-generation H₁-antagonists. In our study, onset of action was estimated to be about 19 min when mTSS was considered, and the difference between active and placebo was significant at 46 min.

Clinical studies of onset of action are few. In a 2-week comparative study of loratadine, astemizole, and placebo, patients assessed the time to clinical relief of symptoms (9). Seventy-three percent in the loratadine group, 32% in the astemizole group, and 19% in the placebo group felt relief of symptoms within 4 h, loratadine thus being significantly superior to astemizole and placebo. However, at the end of the study, there was no significant difference in total symptom reduction between actively and placebo-treated groups; therefore, the data should be interpreted with caution.

Knight (7) has performed a field study in hay fever patients comparing astemizole (10 mg), terfenadine (60 mg), and loratadine (10 mg), with assessment of symptoms every 15 min during the first hour and at hourly intervals for the next 5 h. Onset of relief was determined as the time to 25% reduction of symptom score of any rhinitis symptom and of all common symptoms (sneezing, runny nose, itchy eyes, and stuffy nose). Mean time to relief of any rhinitis symptom was 18 min for all three treatment groups, whereas a 25% reduction in all common symptoms occurred after 4 h with astemizole and 6 h with terfenadine. Less than 50% of the patients in the loratadine group had a 25% reduction from base line within 6 h. Symptoms were alleviated in 69%, 42%,

and 64% of patients treated with astemizole, loratadine, and terfenadine, respectively. It should be emphasized that Knight's study was not placebo-controlled. In our study, the median time to 25% reduction in any symptom was 9 min with acrivastine and 20 min with placebo, and the difference was not significant (data not shown). Furthermore, 71% in P and 91% in A had 25% reduction in total symptom score, bringing into question a 25% reduction in symptoms as a relevant measure of efficacy.

Roman (15) investigated the onset of action of loratadine in seasonal allergic rhinitis. A 59% reduction (mean) in total symptom score appeared 45 min after oral administration of the recommended dose of loratadine, 10 mg; however, the study was not placebo controlled, and allergen exposure was low because the study took place indoors. In our placebo-controlled study, we, on the contrary, had a high natural pollen exposure and found a 22% reduction of mTSS in A and 0% in P at 46 min, and the median time to 50% reduction in TSS was 80 min in A and > 120 min in P. Elucidating differences in time of onset of the different H₁-antagonists can be done only if patients are exposed to the same amount of pollen.

Symptom scoring is highly subjective, and quantitative variables are necessary for an exact estimation of efficacy of treatment and clinical onset of action. A statistically significant difference between A and P in scoring of sneezing was found during the time intervals 31–60 and 61–90 min in number of sneezes. As for rhinorrhea symptoms, counting of nose blowings or quantitation of the mucus by weighing handkerchiefs might have contributed to a more accurate assessment of severity of rhinorrhea than that offered by subjective scoring of symptoms alone. Combining qualitative and quantitative variables might have shown a clinically relevant significant difference in symptoms between active and placebo more exactly.

Although an effect of H₁-antagonists on congestion has occasionally been reported, most clinical H₁-antagonist studies have failed to demonstrate such an effect. In a clinical-pharmacologic study, Gibbs et al. (4) have shown a nasal decongestant effect of acrivastine after histamine challenge, as assessed by a passive rhinometric method. Our study found an effect on congestion. We found a statistically significant rise in nasal peak flow 91–120 min after acrivastine administration, whereas in the placebo group a reduction was demonstrated, but it was statistically significant for only 1–30 min.

A statistically significant difference between A and P was also shown for symptom scoring (median time to 50% reduction in symptom score of congestion) (100 and > 120 min, $P = 0.038$) when we improved

the test power by employing survival analysis and considering excluded patients right censored if missing scores occurred before 50% reduction in symptom score had been reached. However, the efficiency on congestion shown in our study was probably due to a short-term blocking of H₁-receptors on nasal blood vessels, thus repressing the increased blood flow and permeability of vessels caused by histamine from mast cells, rather than to anti-inflammatory properties.

According to the study design, an additional capsule was administered within 1 h if the patient failed to show a 50% reduction in TSS. Thirteen patients of 21 in A and 16 of 18 in P received an additional capsule, and the median time to 50% reduction in total symptom score was 80 min after the first administration of acrivastine 8 mg. We found a statistically significant difference in number of sneezes and nasal peak flow between A and P at 61–90 and 91–120 min, respectively. Whether the achieved efficacy was due to the combined action of both doses is unknown, but this is unlikely, because peak plasma concentration is reached 1.4 h after administration (1).

The concentration of airborne *Poaceae* (grass) pollen has shown two circadian pollination peaks: the first at 0800–1200 and the second at 1600–1800 (11). Our results confirm the expected peak at 0830 (concentration of grass pollen before 0830 not shown), but there was an additional peak from 1130 to 1330. Local measurement of grass pollen the day before the study failed to show an additional increase, and the rise might have been due to activity in the area during these hours. Knowledge of circadian periodicity is important in medical efficacy field studies, and measurement of pollen is essential for control of exposure if the study duration exceeds peak periods and if activity varies in the field.

Pollen counts from Burkard traps placed 15 m above ground and at ground level have shown significant correlation, grass pollen counts being 4.4 times higher at ground level (12). In our study, the pollen ratio ground:roof was 11 at the start of the study and 26 at the end, indicating high exposure to grass pollen.

Exposure time before treatment varied. Twenty-six patients received their first capsule within 30 min, and only four patients did not receive the first capsule within 60 min, suggesting a sufficient exposure of grass pollen in view of patient sensitivity. Treatment was initiated when patients had a TSS ≥ 10 ($\geq 40\%$ of maximum). Differences in graduation of symptoms may have contributed to the delay for the last four patients.

This 1-d field study has several advantages over the more traditional efficacy studies: 1) it is possible to minimize the bias of varying pollen exposure

among patients, 2) comparison and estimation of the clinical onset of action of H_1 -antagonists can be made, 3) it is possible to add objective measures such as counting the number of sneezes, quantitating rhinorrhea, and estimating congestion by nasal peak flow or rhinometric methods.

In summary, acrivastine was shown to be fast-acting and effective in reducing the severity of allergic rhinitis symptoms at high pollen exposure.

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