

Nasal application of a gel formulation of *N*-acetyl-aspartyl glutamic acid (NAAGA) compared with placebo and disodium cromoglycate in the symptomatic treatment of pollinosis*

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A gel formulation of the antiallergic compound *N*-acetyl-aspartyl glutamic acid (NAAGA) (Rhinaaxia® (R)) has been evaluated in a multicenter, randomized, double-blind, three-arm, parallel-group comparison with placebo gel (P) and disodium cromoglycate (DSCG) in outpatients suffering from seasonal allergic rhinitis (pollinosis). Nose and eye symptoms were assessed daily by the patients on visual analog scales (VAS), and medical examinations were held after 1 week and at the end of the 4-week treatment. The use of rescue medications (H_1 -antagonist (terfenadine) and soothing eye-drops (Spersallerg®) was recorded as a main assessment indicator of efficacy. For the efficacy analysis, only the periods with relevant pollen concentrations (≥ 50 grains/m³) were considered. The study extended over the two pollen seasons 1989 and 1990. Of 230 included patients, 190 were suitable for efficacy analysis (R = 63, P = 64, DSCG = 63). The VAS data did not reveal a difference between the treatment groups for nasal symptoms, whereas the use of terfenadine tablets was significantly lower in the Rhinaaxia group than in either the placebo ($P = 0.0001$) or DSCG group ($P = 0.03$). The eye symptoms were significantly less severe in the Rhinaaxia group than in both placebo ($P = 0.0001$) and DSCG ($P < 0.01$) groups. In addition, the use of rescue medication was significantly higher in the placebo than in the Rhinaaxia treatment group ($P = 0.0001$). The incidence of local untoward effects (itching/burning sensation in the nose) was slightly higher in the Rhinaaxia group, while the overall tolerability assessment was similarly good in all three treatment groups. Rhinaaxia gel given three times daily was shown to achieve a satisfactory symptom relief in everyday treatment with a significantly lower need to resort to rescue medication than with placebo and to have a therapeutic effect like DSCG nasal spray given four times daily.

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Rhinaaxia® (Zyma SA, Nyon, Switzerland) contains the magnesium salt of *N*-acetyl-aspartyl

glutamic acid (NAAGA/DCI: spaglumic acid), a dipeptide previously found in the nervous tissue of mammals (7, 19). This dipeptide has an antiallergic effect, as shown by *in vitro* and *in vivo* studies, which is based on three major mechanisms: 1) inhibition of the formation of complement factor C3a and C5a by inhibition of the enzyme C3-convertase (10), 2) inhibition of the release of the leukotrienes B₄, C₄, and D₄ (3), and 3) inhibition of mast cell degranulation (unpublished data). Rhinaaxia nasal solution at the

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daily dose of four to five applications was shown to be effective in the symptomatic treatment of seasonal (8, 11, 16, 17) and perennial (4, 14, 15, 18) allergic rhinitis.

A gel formulation was developed to decrease the dosage by prolonging the duration of contact between the product and the nasal mucosa. Preliminary studies using ^{99}Tc -radiolabeled products showed that the gel remained about three times longer than the solution in the nasal fossae (20). Further clinical comparison proved that three daily applications of the gel were as effective as the solution given five times daily (unpublished data).

It was therefore decided to compare the clinical efficacy and tolerability of Rhinaaxia gel with those of a placebo gel and disodium cromoglycate (Lomusol[®] nasal spray, Fisons) in adult outpatients with seasonal allergic rhinitis (pollinosis).

Patients and methods

This was a multicenter, randomized, three-arm, parallel-group comparison, which was double-blind between Rhinaaxia gel and its placebo gel, and open between the gel and DSCG, since no double-dummy method was practicable. All three study drugs were packed into neutral metered-dose bottles. Rhinaaxia gel delivered 8.4 mg Mg-NAAGA decahydrate at each actuation. The placebo gel had exactly the same galenic formulation, except for the absence of active substance. The DSCG 2% nasal spray was obtained from commercially available Lomusol nasal spray and then transferred into the study bottles.

The purpose and methods of the study were approved by the ethics committee of the University Hospital of Bern. Adult outpatients complaining of seasonal rhinoconjunctivitis were evaluated regarding the inclusion and exclusion criteria. The following reasons were cause for exclusion: nonallergic or nonseasonal rhinitis, chronic sinusitis, or chronic asthma; ongoing desensitization therapy; vacations outside Switzerland during the trial; ongoing use of any type of anti-inflammatory drugs; and recent use of depot corticosteroids or astemizole (within 2 months), or short-acting steroids (within 2 weeks). For women, pregnancy, breast feeding, or contraceptive measures other than birth control pill or IUD were further exclusion criteria. After the patient's informed consent was obtained, the allergic origin of the current symptoms was verified by means of either RAST or skin prick tests (for tree and grass pollen). The patients were then allocated to one of the three treatments (Rhinaaxia gel, one puff in each nostril three times daily, placebo three times daily, or DSCG four times daily, according to a computer-generated randomization code (blocks of six). The treatment duration was 4 weeks, with a

visit scheduled after 7 d (intermediate) and 28 d (final visit).

If relief of nasal symptoms was perceived as insufficient by the patient, the intake of 60-mg terfenadine tablets was allowed, while Spersallerg[®] eye-drops were available to soothe possible eye discomfort. Recording of this rescue medication was part of the instructions to the patient, as the use of medication was a main factor in assessing efficacy.

Efficacy and tolerability were determined by both patients' and doctors' individual assessment. Discomfort of the nose and eye as felt by the patient was evaluated daily by means of two separate 100-mm visual analog scales (VAS) on diary cards, with the wording "none" at the left and "worse than ever" at the right side. The distance in mm from the left side to the mark that the patient ticked was used for the analysis of discomfort.

In addition to the subjective evaluation, the doctor assessed at each of the three visits the intensity of symptoms as described by or observed in the patient. The medical evaluation comprised the assessment of three nose symptoms ("stuffiness", "sneezing", and "nasal discharge") and three eye symptoms ("redness", "watering", and "itching"), according to appropriate 4-point intensity scales.

On days 7 and 28, patients and doctors had to give separately their overall impression of the treatment efficacy (5-point scale from "very marked improvement" to "worsening of the condition"). The tolerability issues were considered at the patient level (space on the diary card for recording any "unwanted effect") and at the investigator level (active search for "adverse reactions" at each visit and global evaluation of tolerability at the final evaluation).

As patients were recruited from all over Switzerland, daily pollen measurements from 10 different geographic points were taken into account for the allergen exposure.

Statistics

Statistical methods. The null hypothesis (H_0) was that there was no difference between the treatment groups. The one comparison concerned Rhinaaxia gel and its placebo; the other, Rhinaaxia gel and DSCG. The two-sided P value of the α risk for rejecting H_0 was set at $P=0.05$. Any lower P value was reported as statistically significant.

The statistical analysis was performed by the SAS statistical software version 6 of SAS Institute, Inc (Cary, NC, USA). The following tests were used for the statistical analysis. 1) On the VAS and on the rescue medication intake, the general linear model (GLM) procedure was used. The VAS was averaged per day from the days where the pollen count was ≥ 50 grains/m³ (generally accepted as the triggering

threshold of symptoms). 2) On the quantitative demographic variable (age), the ANOVA was used, whereas on the qualitative variable (sex) the chi-square test was used.

Results

A total of 230 patients were enrolled in the study. Of them, 40 had to be excluded from the efficacy analysis for various reasons (negative RAST, use of unpermitted medications, lack of compliance with the protocol, underuse of test drug, lost to follow-up, etc.). The 190 patients suitable for efficacy analysis were evenly distributed among the groups (Rhinaaxia = 63, placebo = 64, DSCG = 63).

The treatment groups were comparable in distribution by sex, age, medical history, and average severity of symptoms of rhinoconjunctivitis. The reported eye symptoms were generally less severe than for the nose (Table 1). Twenty patients withdrew from the trial for various reasons (lack of efficacy: two; adverse events: eight; disappearance of symptoms: two; unknown: eight).

Efficacy

When the evolution of symptoms throughout the observation period was exclusively considered, their severity was observed to decrease steadily in all three groups.

Since the study was performed in various parts of Switzerland, with different pollen burdens and different length of the pollen seasons, the symptoms of the patients were considered only when the pollen concentration was ≥ 50 grains/m³ of air in the relevant geographic areas. Indeed, a detailed analysis of VAS and of adjunct drug intake as a function of pollen count revealed that both symptoms and use of rescue medication correlated to the grass pollen level.

The mean values for nose discomfort were not

Table 1. Characteristics of patients suitable for efficacy

	NAAGA n=63	Placebo n=64	DSCG n=63
Sex M	38	37	29
F	24	25	34
(missing 3)			
Age Mean	31.5 yr	32.3 yr	32.3 yr
Range	(18–53)	(18–60)	(18–51)
(missing 4)			
Diagnosis of allergy since:			
Mean	9.5 yr	12.3 yr	12.1 yr
(missing 4)			
Sum of scores (SD)			
– Nose symptoms	6.3 (± 2.2)	6.4 (± 2.2)	6.2 (± 2.0)
– Eye symptoms	4.2 (± 2.7)	3.9 (± 2.7)	3.9 (± 2.8)

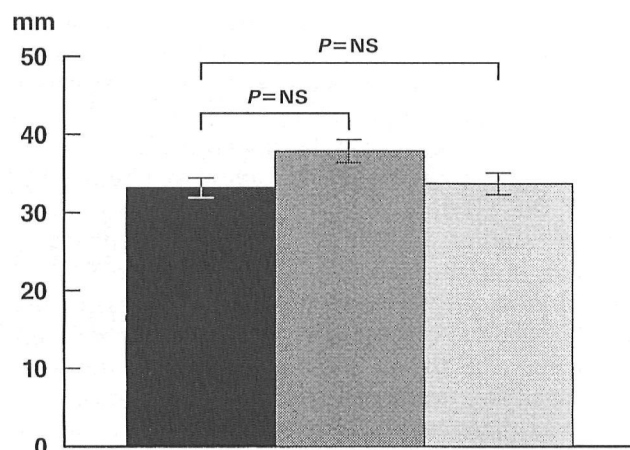


Fig. 1. Severity of nasal discomfort as assessed daily by patients on VAS (mean $\pm$ SEM).

statistically different among the treatment groups, whereas the consumption of rescue medication was clearly higher in the placebo than in the two other treatment groups (Figs. 1 and 2). Neither the intermediate nor the final medical examinations revealed a between-group difference in severity scores for both nose and eyes, as judged by the investigator.

The eye symptoms were also different among the groups, the lowest VAS mean value appearing in the Rhinaaxia gel group (Fig. 3). Nevertheless, the use of soothing eye-drops was, on average, far more important in the two other treatment groups (Fig. 4). By covariance analysis (covariate = rescue medication), it was found that VAS for nose and eyes actually differed among the treatment groups, favoring Rhinaaxia gel over placebo for both nose ($P = 0.035$) and eye ($P = 0.0001$), and over DSCG for eye discomfort ($P = 0.009$).

Regarding tolerability, adverse effects were reported by 17, 14, and 11 patients treated by Rhi-

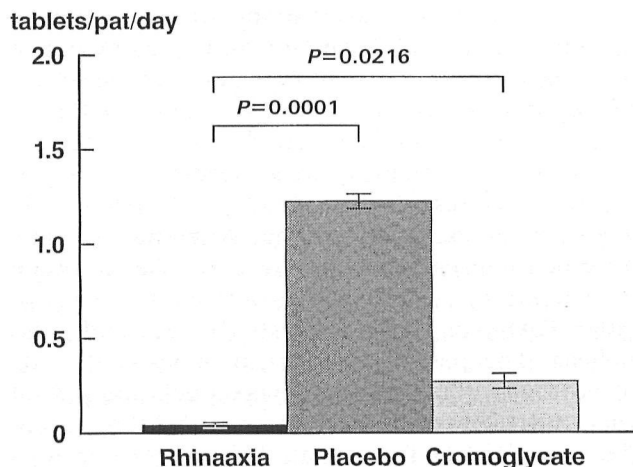


Fig. 2. Daily use of 60-mg terfenadine tablets as rescue medication for nasal symptoms (mean $\pm$ SEM).

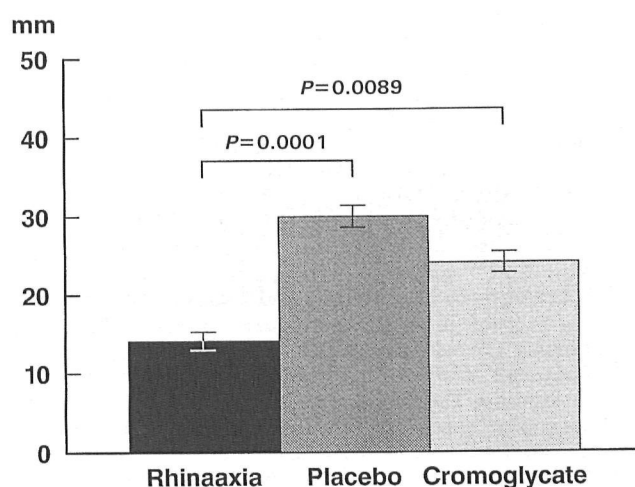


Fig. 3. Severity of ocular discomfort as assessed daily by patients on VAS (mean $\pm$ SEM).

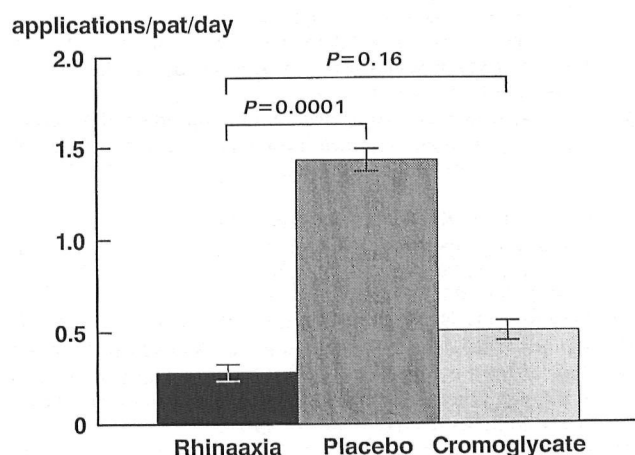


Fig. 4. Daily use of Spersallerg soothing eye-drops as rescue medication (mean $\pm$ SEM).

naaxia gel, placebo, and DSCG, respectively. Irritation of the nose was the most frequent complaint, with the highest incidence in the Rhinaaxia gel recipients. On the other hand, only DSCG was linked with the report of gastrointestinal disturbances (Table 2).

Table 2. Adverse events (without causal relationship assessment)

Type	Rhinaaxia	Placebo	DSCG
Nose symptoms	20 (3)	13 (1)	6 (1)
Eye symptoms	2	0	1
Mouth and throat symptoms	2	1	3 (1)
CNS symptoms	3	3	3 (1)
Lung symptoms	1	1	1
Gastrointestinal symptoms	0	0	3
Miscellaneous	1	0	0
Number of patients reporting ADEs	17	14	11

()=number of withdrawals caused by side-effects.

The untoward effects were mild and transient in most cases, and no serious adverse event occurred during the trial. Adverse drug reactions led to termination of the treatment by three Rhinaaxia gel-, one placebo-, and four DSCG-treated patients. In the global evaluation of tolerability, all three treatments were rated as "very good" or "good" by more than 90% of the patients.

Discussion

The main aim of this study was to investigate the clinical efficacy and tolerability of Rhinaaxia gel by comparing it simultaneously with its matching placebo and the well-established antiallergic drug DSCG.

While the direct comparison with the placebo gel could be kept double-blind, both the formulation (spray) and the recommended daily dose of DSCG/Lomusol did not enable us to obtain an optimal design for all three arms of this comparative trial.

Because of the geographic and meteorologic factors, the conditions of pollen exposure were unsteady, leading to quite variable symptoms during the study period. Therefore, the commonest denominator for all the patients was the measurable pollen concentration in the air. The concentration of 50 grains/m³ is a widely accepted threshold above which the symptoms of allergic rhinoconjunctivitis are elicited in most patients (2, 6, 9, 21). Indeed, the reliability of the data obtained in different centers was supported by a good correlation between symptom severity or rescue drug intake and pollen exposure in all three treatment groups.

In this trial, the nose symptoms as assessed by the patients were, on average, not different among the three treatment groups. On the other hand, the average intake of the oral antihistamine terfenadine was significantly lower in the two groups on active treatment. It could thus be assumed that a major influence was exerted by the rescue medications on the severity of symptoms, and this was confirmed by the analysis of covariance. Quite similar observations had already been made with Rhinaaxia nasal spray (16).

In contrast to nasal symptoms, eye complaints were, on average, more severe in the placebo- and the DSCG-treated patients, although soothing eye-drops were used more in the two comparative groups. Such an improvement of eye symptoms with nasally applied drugs is not unusual, as the drugs might have reduced the swelling of the nasal mucosa and thus improved the outflow of the lacrymal duct. The possible effect at the level of the nasal mucosa could not explain a more global effect (i.e., decrease of itching and redness of the eye). It is not known whether the demonstrated systemic absorption of NAAGA (un-

published data) could really act on eye mast cells. If so, it is certain that less proinflammation mediators (histamine, leukotrienes) would be released at the level of the eye conjunctiva (5, 12). In this context, previous studies with Rhinaaxia nasal solution have already shown nasal blockage to be significantly reduced (11, 13), and ocular symptoms to decrease more rapidly than with DSCG (8) or to decrease in parallel with nose symptoms (1). The intermediate and final medical examinations did not detect a difference between the treatment groups. However, these examinations were performed irrespective of the pollen count in the air. These data indicate that Rhinaaxia gel was superior to placebo gel, and of the same efficacy as DSCG in the symptomatic treatment of allergic rhinitis.

In addition, the superiority of the Rhinaaxia gel over placebo proves that its efficacy does not rest simply on a possible mechanical barrier function of the gel base against airborne allergenic particles. The active substance NAAGA does therefore account for the main part of the therapeutic effect.

From the tolerability point of view, the untoward effects of the drugs were similar. Only nasal irritation was more frequent in the Rhinaaxia gel group. As most of the reported adverse reactions were rather mild and transient, it was not surprising to find the overall judgment of tolerability to be positive in more than 90% of the patients in each group.

It may be therefore concluded that for seasonal allergic rhinitis Rhinaaxia gel applied three times a day was demonstrated under everyday treatment conditions to have a therapeutic effect like that of DSCG nasal spray applied four times a day and to achieve satisfactory symptom relief without adjunct therapy. Although nasal irritation was slightly more frequent with Rhinaaxia gel, the perception of overall tolerability was similar in all three treatment groups.

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