

Short communication

The protective effect of *N*-acetyl-aspartyl-glutamate (NAAGA) against nasal obstruction provoked by antigen in allergic rhinitis

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P. Magyar, Z. Györi, Z. Márk, I. Hutás

Department of Pulmonology, Semmelweis Medical University, Budapest, Hungary

Specific nasal challenge test (NCT) with pollen extracts was performed before and after a single dose pretreatment with *N*-acetyl-aspartyl-glutamate (NAAGA: Rhinaaxia®) nasal spray in 11 grass- and ragweed-pollen-sensitive patients with allergic rhinitis in symptom-free condition to test the protective effect of this drug on allergen-induced nasal obstruction and symptoms. In 7 of 11 patients, a third NCT was performed in the same way as the second one, except that placebo spray was used for pretreatment instead of NAAGA nasal spray. Nasal airways resistance (R_{nas}) measurements were performed before pretreatment and 15 min after NCT. Pretreatment with NAAGA 1 h before NCT significantly ($P < 0.001$) attenuated antigen-induced nasal obstruction. The mean protection was 64%. The protective effect against nasal symptoms was likewise significant ($P < 0.001$), but the mean protection was found to be essentially lower (39%) than for R_{nas} . Pretreatment with placebo nasal spray showed only a 13% ($P > 0.1$) protection for R_{nas} , while it did not decrease allergen-induced nasal symptoms. The results suggest that the favorable effect of the regular administration of NAAGA in allergic rhinitis is to be expected primarily when the main complaint is nasal obstruction.

Key words: grass pollen; nasal challenge; nasal obstruction; *N*-acetyl-aspartyl-glutamate; ragweed pollen.

Dr P. Magyar
Department of Pulmonology
Semmelweis Medical University
Budapest
Hungary

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NAAGA, *N*-acetyl-aspartyl-glutaminic acid, is a dipeptide, a 2:1 mixture of its alpha and beta isomers. The magnesium salt of NAAGA (Rhinaaxia®, Leclerc & Co, Schaffhausen, Switzerland, licensed by Transphyto SA, Clermont-Ferrand, France) has been reported to be advantageous in the treatment of allergic rhinitis, when used as nasal spray (7, 8).

NAAGA, a naturally occurring dipeptide, was first isolated from rabbit brain (4). It was later found in the brain of numerous mammals, including man (2). The compound inhibits mast cell degranulation of anaphylactic or nonanaphylactic origin and the synthesis of certain leukotrienes, as well as the activation of the complement cascade (1, 3, 5, 9). By means of the last effect, it inhibits the development

of the inflammatory mediators C3a and C5a, as well as of the membrane-damaging complexes C5-C9.

The aim of the present study was to determine whether and to what extent NAAGA given in a single conventional therapeutic dose of two puffs in each nostril (one puff (0.07 ml) delivers 4.2 mg active substance) inhibits severe nasal obstruction and symptoms provoked by pollen solution.

Patients and methods

Eleven patients with seasonal rhinitis (aged 20–47 years, mean age 33.4 years, four men and seven women) whose diagnosis was based on the case his-

tory, previous clinical symptoms, and positive skin test with pollen solution (Soluprick®, Epipharm) were admitted to the study after giving informed consent. Sensitivity to grass pollen was found in three patients and to ragweed in eight patients. Acute or chronic sinusitis, or any other disease had not been observed.

Nasal challenge test (NCT) was performed in asymptomatic patients 1–4 months before the assumed appearance of the seasonal symptoms.

Based on the pollen sensitivity, NCT was performed with 1:100 dilution of Soluprick ragweed and the undiluted grass-pollen mixture solution (Graser-Mix 100 000 SQ-U/ml) by dripping one drop into each nostril of the patient with the head bent backwards.

NCT was repeated 7–10 d after the first day under identical conditions and at the same time of the day 1 h after administering two puffs of NAAGA nasal spray into each nostril.

In 7 of 11 patients, a third specific NCT was performed in the same way: a placebo spray (solution of the same composition except NAAGA) was used for pretreatment instead of NAAGA nasal spray. The former spray (placebo) had the same appearance as the latter.

Measurement of the R_{nas} reflecting nasal obstruction was performed with a volume-stable body plethysmograph (Body Test, Erich Jäger, Würzburg, Germany) directly before pretreatment with either NAAGA or placebo and 15 min after NCT. The R_{nas} value was obtained from the difference between airway resistances measured during nasal breathing through a face mask and during oral breathing through a mouthpiece while the nose was clamped. The strength of the provoked nasal symptoms (itching, rhinorrhea, sneezing) was graded 0 and 1–3, respectively, and it served as a global symptom score 15 min after provocation.

Student's t-test was used for statistical analysis of the data.

Results

R_{nas} values before and 1 h after pretreatment with either NAAGA or placebo did not differ significantly.

The R_{nas} values measured before nasal provocation without and with NAAGA pretreatment showed no significant differences ($R_{nas} = 0.44 \pm 0.15$ and $0.40 \pm 0.13 \text{ kPa} \cdot \text{l}^{-1} \cdot \text{s}$). After NCT performed without NAAGA pretreatment, the mean R_{nas} value exhibited more than sixfold increase ($P < 0.001$). The increase in R_{nas} after NCT was significantly lower ($P < 0.001$) with NAAGA pretreatment (Fig. 1). The protective action was found to be $64 \pm 30\%$. The protective effect against R_{nas} increase was negligible

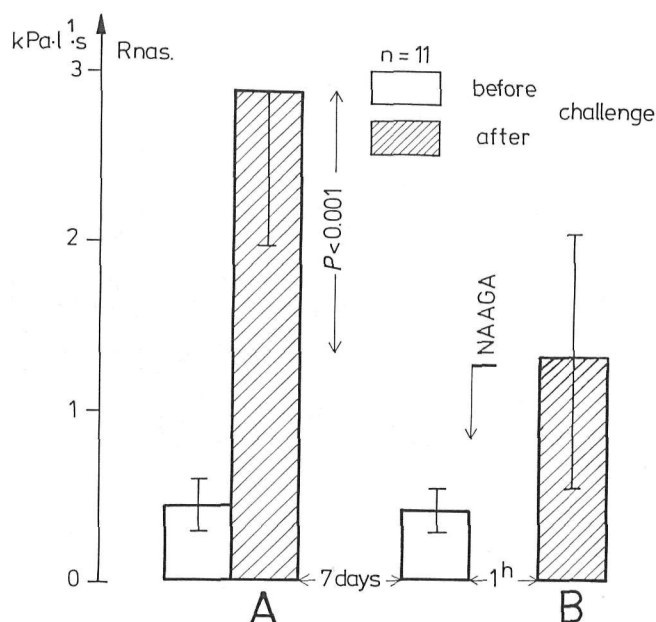


Fig. 1. Mean changes and standard deviations of nasal resistance (R_{nas}) after specific nasal challenge tests (NCT) without (A) and with NAAGA (B) pretreatment in patients with allergic rhinitis.

(below 20%) in only two of the 11 cases. Pretreatment with placebo nasal spray showed only 13% ($P > 0.1$) protection against antigen-induced R_{nas} increase.

The intensity of nasal symptoms observed by both the patient and the physician was, except in one case, always lower after provocation performed after NAAGA pretreatment than without pretreatment. Although the mean protective effect against the intensity of the provoked symptoms after NAAGA

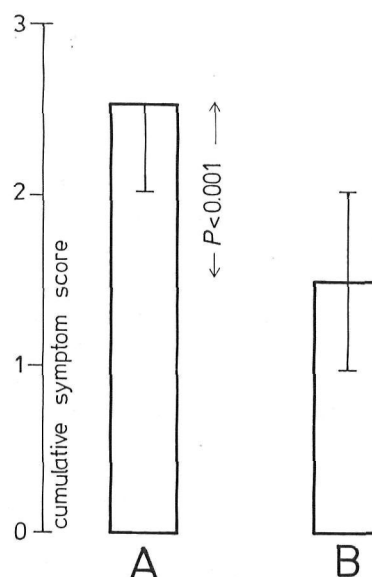


Fig. 2. Mean values and standard deviations of global symptom scores after specific NCT without (A) and with NAAGA (B) pretreatment.

pretreatment was significant (39.4%; $P < 0.001$) (Fig. 2), it did not reach the level of the effect inhibiting R_{nas} increase. Pretreatment with placebo did not have any protective effect against allergen-induced nasal symptoms.

Discussion

The results of the present study unambiguously demonstrate that NAAGA has a significant protective effect against nasal obstruction provoked by pollen antigen.

The mean 64% protection is double that found by Ghaem (6) 20 min after NCT with grass pollen extract (four grass pollens, Institut Pasteur, Paris, France) after the administration of an identical single NAAGA dose. The lower effect is presumably due to the difference in the study protocols, and not to the difference in the pollen extracts used. In Ghaem's examination, NCT was performed half an hour, and not 1 h, after the administration of NAAGA, suggesting that more than half an hour is required to obtain the maximum protective effect. The degree of the provoked nasal obstruction is another difference. Our aim was to provoke as far as possible nasal obstruction and symptoms characteristic of severe rhinitis during the pollen season. Therefore we used relatively high antigen doses which produced a six-fold increase in R_{nas} 20 min after NCT, while only a two- or threefold increase (from 0.27 to 0.63 kPa $\cdot$ l $\cdot$ s $^{-1}$) was provoked in Ghaem's study (6). Nonetheless, it seems unlikely that by increasing the provoked obstruction the protective effect of the identical NAAGA dose would be increased. Instead, the opposite could be assumed. The global symptom score of itching, rhinorrhea, and sneezing after baseline NCT rose to 2.54 (the chosen highest score being 3) indicates that pronounced symptoms, observed only in severe rhinitis during the pollen season, could be induced in a short time in asymptomatic patients. Contrary to other reports (6), we observed the unambiguous improvement of these symptoms after the administration of NAAGA, although the extent of the protective effect (39%) was essentially lower than observed for R_{nas} . However, this represents no contradiction, since sneezing and rhinorrhea are reflex-mediated processes, while nasal obstruction is the consequence of vasodilation and mucosal edema (10). Accordingly, a drug does not

necessarily protect to the same extent against R_{nas} increase and nasal symptoms.

The reverse can be observed with H_1 antihistamines. Their improving effect on nasal resistance lags substantially behind symptomatic improvement (10). Accordingly, NAAGA and H_1 antihistaminic compounds (terfenadine, ketotifen, mequitazine) fairly complement each other in cases where improvement has not been satisfactory after monotherapy.

The results of the present study suggest that the favorable effect of the regular administration of NAAGA is to be expected primarily when the main complaint is nasal obstruction.

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