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Clinical efficacy of *N*-acetyl-aspartyl-glutamic acid nasal spray in children suffering from pollinosis: A double-blind multicentre study*

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SUMMARY

A double-blind, four-centre study was carried out in 66 children to compare the clinical efficacy and safety of N-acetyl-aspartyl-glutamic acid (NAAGA) and disodium cromoglycate (DSCG) nasal sprays. At similar dosage conditions (one puff per nostril, four times daily, for 3 weeks), no significant differences between the treatments were discernible in the primary efficacy parameters (scores, patients' and physicians' opinion). Both products induced statistically significant improvements in the nasal, ocular and total scores, but not in the respiratory (breathing) score. The hay-fever symptoms improved clinically in >50% of the children after only two weeks with both treatments. The exact figures depended on the parameters considered. Thirteen out of 25 patients (52%) in the NAAGA group found the efficacy "good" or "excellent" at the end of the treatment period; the corresponding opinion in the DSCG group was expressed by 10 out of 24 patients (41.7%). Of the 28 patients that used the rescue medication, 12 (42.8%) were from the NAAGA group and 16 (57.1%) from the DSCG group. One patient on NAAGA treatment reported side effects, i.e. pruritus in the nose and sneezing.

Key words: perennial allergic rhinitis, pollinosis, anti-allergic drugs, nasal sprays

INTRODUCTION

Rhinaaxia (Zy 15106) is a new anti-allergic agent used in the prevention and treatment of seasonal and perennial allergic rhinitis. The active substance is the magnesium salt of *N*-acetyl-aspartyl-glutamic acid (NAAGA), a natural dipeptide found in the human brain.

The reported pharmacological properties of NAAGA are: (1) inhibition of mast cell degranulation (Fricke and Gaus, 1986); and (2) an inhibitory effect on complement activation, including inhibition of the production of anaphylactoxins C_3a and C_5a (Chevance and Etiévant, 1986; Etiévant et al., 1988) and inhibition of the anaphylactic release of leukotrienes B_4, C_4 and D_4 (SRS-A; Bastide et al., 1987). A significant reduction of the symptoms of allergic rhinitis (both perennial and seasonal) in adults has been amply demonstrated with topical use of Rhinaaxia (Ghiringhelli, 1986; Girard and Weibel, 1987, 1989; Datz et al., 1988; Blamoutier and Luyckx, 1988; Gastpar et al., 1989; Harnest et al., 1989).

The aim of this study was to evaluate the clinical efficacy of NAAGA nasal spray and to compare it to that of disodium cromoglycate (DSCG) nasal spray in children suffering from pollinosis.

PATIENTS AND METHODS

Design of the study

The study was double-blind, parallel, randomized and multicentered (four centres: Liège, Brussels, Ghent and Yvoir in Belgium).

Patients

Sixty-six children (age: 4-16 years) suffering from pollinosis as evidenced by acute symptoms at entry (rhinorrhoea, nasal obstruction and sneezing) and a history of allergic reaction to pollen (confirmed by prick test), were selected for the study. Children with systemic disease, chronic respiratory diseases (non-allergic rhinitis, sinusitis, and asthma) and those on recent

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(two weeks prior to) de-sensitization, corticosteroid or astemizole treatments were excluded.

Medication

NAAGA (Rhinaaxia; 6% solution containing 8.4 mg of the active substance) and DSCG (Lomusol; 2% solution providing 2.8 mg of the active substance) metered-microdose sprays were identical in appearance and both released 0.14 ml of solution per puff. The dosage was one puff per nostril, four times daily for three weeks. Terfenadine suspension (30 mg/50 ml) was used as a rescue medication if the symptoms did not improve on day 3. Each administration of the terfenadine suspension and the reason for its use were noted in the patient's diary.

Evaluation criteria

The parameters for evaluation are shown in Table 1. All symptoms were scored on a 4-point scale and recorded by the physician on days 0, 14, and 21.

Table 1. Comparative efficacy and safety of NAAGA and DSCG nasal sprays in children suffering from pollinosis.

evaluation criteria		treatments (N)	
		NAAGA	DSCG
1. scores:	1.1 nasal		
	- blocked nose		
	- rhinorrhoea		
	- sneezing		
	1.2 ocular		
	- itchy eyes	no significant differences	
	- lacrimation	(see Figure 1)	
	1.3 respiratory		
	- cough		
	- dyspnoea		
	1.4 total		
2. physician's opinion(points)		patients X	points
	2.1 null (0)	0	0
	2.2 fair (1)	6	6
	2.3 satisfactory (2)	10	2
	2.4 good (3)	18	18
	2.5 excellent (4)	16	16
	mean points	total points ÷ number of patients	
		2.00	1.75
3. patient's opinion (points)		patients X	points
	3.1 null (0)	0	0
	3.2 fair (1)	5	6
	3.3 satisfactory (2)	8	6
	3.4 good (3)	24	6
	3.5 excellent (4)	20	32
	mean points	total points ÷ number of patients	
		2.28	2.08
4. use of rescue medication			
number of patients		12	16
5. withdrawal of treatment			
(number of patients, cause)		1	1
poor therapeutique response		lack of efficacy	
side effects:			
- pruritus			
- sneezing			

Ethical considerations

The patient's parents were informed about the reason and the modalities of the trial and were asked to give their written consent. The protocol was approved by the Local Ethical Committee.

Statistical analysis

To compare the data of both groups a Chi-square test (with Yates correction), a Student's t-test (for variables with a normal distribution) or a Mann-Whitney rank test (for variables without a normal distribution) were used. ANOVA was used in case of homogeneity of the variances.

Intragroup comparisons were performed with the aid of the paired Student's t-test (for a normal distribution) or the Wilcoxon matched-pairs test (for a non-Gaussian distribution). For the evaluation of homogeneity of variance the Levene and Bartlett-Box tests were used; Lilliefors was the test used for normality.

RESULTS AND DISCUSSION

Of the 66 case record forms, 64 were analysed for safety and 52 for efficacy. Fourteen children were excluded from the analysis because of various reasons, such as: (1) older than 16 years; (2) no symptoms at entry visit; (3) failure to attend on the second and third visits; (4) use of nasal vasoconstrictors; (5) nasal Vicks; (6) use of anti-histaminic drugs; and (7) use of DSCG and NAAXIA eye drops.

No significant differences between the centres (p=0.17), nor between the groups (p=0.85) were detected ensuring comparability and ruling out seasonal, centre or group biases in the study.

The results for comparative efficacy and safety of the test (NAAGA) and control (DSCG) treatments are presented in Table 1 and Figure 1. Analysis of the primary efficacy parameters between treatments (Table 2) revealed no significant intergroup differences. Both products induced statistically significant improvements of the nasal, ocular and total scores, but not of the breathing scores. This is not surprising since

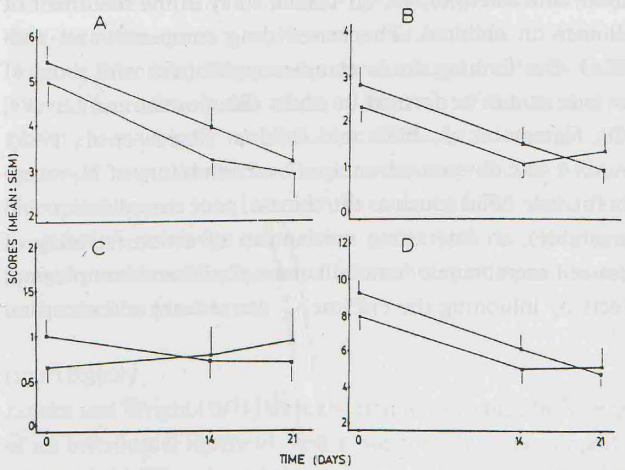

Figure 1. Improvement in nasal (A), ocular (B) and total scores (D). Breathing scorse (C) are not improved. "x" signifies NAAGA-treated patients; squares represent DSCG-treated patients. Values (mean ± SEM) from clinical record forms..

coughing, dyspnoea and oppression are not typical manifestations of hay fever. The hay-fever symptoms improved clinically in >50% of the children after only two weeks with both therapies. The exact figures depended on the parameters considered. Thirteen out of 25 patients (52%) and 10 out of 25 physicians (40%) from the NAAGA group and 10 out of 24 patients (41.7%) and 10 out of 24 physicians (41.7%) from the DSCG group rated the efficacy "good" or "excellent" at the end of the treatment period. The patients' diaries confirmed the results supplied by the case record forms and revealed no differences between NAAGA and DSCG.

The parameter involving the use of rescue medication showed a trend in favour of NAAGA nasal spray. No serious side effects were detected. Of the 64 patients (33 on NAAGA, and 31 on DSCG) included in the safety analysis, one patient on NAAGA treatment reported pruritus in the nose and sneezing. Because of this finding and the poor therapeutical effect in this patient, the therapy with NAAGA nasal spray was discontinued after a period of eight days.

Table 2. Results of the primary efficacy parameters between treatment groups.

	clinical record form		patient's diary	
parameter results	visit 0	visit 1	visit 2	global
	(day 0)	(day 14)	day (21)	(day 1 to 21)
scores:				
nasal	NS	NS	NS	NS
ocular	NS	NS	NS	NS
breathing	NS	NS	NS	-
total	NS	TR*	NS	NS
patient's opinion	-	NS	NS	-
physician's opinion	-	NS	NS	-

* Trend ($p = 0.086$) in your favour of NAAGA

The results of this double-blind comparative trial confirm the efficacy and safety of NAAGA nasal spray in the treatment of pollinosis in children. The tested drug compared well with DSCG. Our findings are in complete agreement with those of previous studies performed in adults (Blamoutier and Luyckx, 1988; Harnest et al., 1989) and children (Paupe et al., 1988). NAAGA has obvious advantages over inhibitors of H_1-receptors (no side effects such as drowsiness, poor co-ordination and excitability), an interesting mechanism of action (stability of mast-cell membranes, "anti-leukotriene" and anti-complement effects by inhibiting the enzyme C_3-convertase) and comparability with DSCG (whose properties are well-established for efficacy and safety), and consequently promises to be a useful drug in the treatment of pollinosis.

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