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A cross-over comparison of acrivastine, pseudoephedrine and their combination in seasonal allergic rhinitis

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SUMMARY

In a four period, double-blind cross-over study, forty patients with moderate to severe symptoms of seasonal allergic rhinitis received in randomised order 8 mg acrivastine, 60 mg pseudoephedrine, 8 mg acrivastine plus 60 mg pseudoephedrine and placebo. Each treatment was given three times daily for six days with a one day washout period between treatments.

Acrivastine alone significantly reduced all the symptom severity scores when compared to placebo or pseudoephedrine alone ($p < 0.01$). These severity scores were assigned daily by patients for itchy nose/throat, sneezing, running nose, blocked nose, watery eyes, itchy eyes and overall symptoms. The combination of acrivastine and pseudoephedrine was significantly better than either placebo or pseudoephedrine alone in controlling all symptom scores ($p < 0.01$) and it was also superior to acrivastine alone ($p < 0.05$) in controlling all symptoms except itchy eyes. The results confirm the expected additive rather than synergistic effect of acrivastine and pseudoephedrine in combination.

The control of symptoms assessed at the end of each treatment period was considered either excellent or good by 79% of patients and 84% of investigators for acrivastine plus pseudoephedrine and, for acrivastine alone, by 69% of patients and 67% of investigators.

Both acrivastine alone and acrivastine and pseudoephedrine in combination were well tolerated. There was no significant difference in the number of adverse experiences reported in either of these two groups compared to the number of adverse experiences reported in the placebo group.

INTRODUCTION

The symptoms of seasonal allergic rhinitis include those caused by histamine release, causing rhinoconjunctivitis, and nasal congestion. Antihistamines which

block the H_1 receptor site are widely used in the treatment of seasonal allergic rhinitis (hay fever) although the effect on nasal congestion is often minimal. Consequently combination products including a sympathomimetic such as pseudoephedrine are often preferred since rapid vasoconstruction results in nasal decongestion.

Acrivastine is a new antihistamine (Cohen et al., 1985a) which offers a significant benefit in the management of seasonal allergic rhinitis (Bruno et al., 1986, 1989; Gervais et al., 1989). The purpose of the study was to determine the efficacy and safety of multiple doses of acrivastine combined with pseudoephedrine in comparison with that of either agent alone.

METHODS

This study was carried out between April and July in 1984 by Dr. A. Meran, Steinenvorstadt 19, 4051 Basel, Switzerland.

Patients with a clinical history of seasonal allergic rhinitis over a period of several years were eligible for trial entry. The allergic basis of their symptoms had been demonstrated within the preceding two years by producing a weal on skin testing with mixed grasses at least 3 mm in diameter greater than the saline control. Patients were required to be free of other acute or chronic disease or nasal deformity, to have normal pulse and blood pressure and to be within the 12–70 year age band. Women of child bearing potential who were pregnant, nursing or not adequately protected by contraceptive measures were excluded, as were patients required to drive or operate dangerous machinery as part of their employment.

The cross-over study was divided into four consecutive periods each consisting of six days of treatment during which trial medication was taken three times daily followed by a one day washout period.

The treatments were: acrivastine 8 mg; pseudoephedrine 60 mg; acrivastine 8 mg and pseudoephedrine 60 mg in combination; placebo.

The order of treatments was randomised according to a Latin square design and double-blinding was achieved by using the "double-dummy" technique. All other medication for hay fever was discontinued at appropriate intervals prior to trial entry. Systemic corticosteroids were prohibited one month prior to and throughout the study. Nasal cromoglycate and corticosteroids were prohibited seven days prior to and throughout the study while antihistamines, anti-allergics and decongestants were prohibited 24 hours prior to and throughout the study.

At the initial screening, following a full medical history, physical examination and provision of verbal consent by the patient, the investigator assessed the symptoms of hay fever as mild, moderate or severe. On trial entry patients were provided with appropriate medication for the first treatment period and a diary

card, on which they were requested to record at the end of each day the severity of six symptoms of hay fever and the overall severity of all symptoms, according to the following scheme:

0 = no symptoms
1 or 2 = slight
3 or 4 = moderate
5 or 6 = severe
7, 8 or 9 = very severe.

At the end of each treatment period patients returned to the clinic (seventh day) when the investigator assessed the efficacy of treatment as either excellent, good, satisfactory, poor or abysmal and recorded the incidence of adverse experiences, either reported spontaneously or following indirect questioning. Patients also provided an assessment of treatment efficacy and were asked if they would continue treatment if that particular treatment were available. Diary cards and medication for the next treatment period were issued and the study procedure was repeated.

RESULTS

Forty patients entered the study which commenced at the end of April 1984. Demographic details are given in Table 1. All but three were suffering from seasonal allergic rhinitis. The three exceptions had perennial rhinitis but with positive skin tests to grass. The severity of all the patients' symptoms at trial entry was graded by the investigator on a scale from 1-3 (mild, moderate, severe): the mean was 2.6 (se = 0.09).

Study withdrawals

Five patients did not complete all four treatment periods; data collected for these patients up to the time of withdrawal have been included in the analyses. Three patients withdrew due to lack of treatment effect and when the code was broken

Table 1. Demographic details.

male		15
females		25
age (years)	- mean	28
	- range	17-56
weight (kg)	- mean	64
	- range	52-89
height (cm)	- mean	167
	- range	146-182
pre-trial symptoms	- mild	1
	- moderate	13
	- severe	26

all three had been taking placebo at time of withdrawal. One patient had to withdraw at the end of the third treatment period as he was leaving the country. The fifth patient suffered greatly from her hay fever symptoms during treatment period 1 (placebo) and complained of headaches. At the end of the second treatment period (pseudoephedrine) the patient rated her symptom control as poor and also complained of headaches, nausea and insomnia. The patient was withdrawn from the study and referred to a neurologist for a second opinion regarding the headaches; the adverse reactions were assessed as possibly related to pseudoephedrine.

Symptom assessments

The mean severity score for the six symptoms, sneezing, itchy nose/throat, running nose, blocked nose, watery eyes and itchy eyes and the overall symptoms was calculated over each of the six day treatment periods. The mean scores for each symptom were analysed by the analysis of variance with subject, occasion and treatment as factors. The mean scores were log transformed in order to meet the distributional assumptions of the analysis of variance. The treatment means were compared using the Newman-Keuls multiple range test (Newman, 1939; Keuls, 1952) and are given in Table 2. Figure 1 illustrates graphically the mean daily transformed severity score for the overall assessment of symptoms, the pattern of which was representative of the patterns for each individual symptom. When taking placebo patients consistently produced higher symptom scores, reflecting more severe symptoms, than they did when taking any of the three other treatments. The mean scores could be ranked in the same way for all

Table 2. Overall mean transformed scores.

	placebo	pseud.	acr.	acr. + pseud.	standard error of difference
sneezing	3.50	3.18	2.48**	1.60**	0.21
itchy nose/throat	3.34	2.96	2.24**	1.51**	0.23
running nose	3.47	3.06*	2.46**	1.79**	0.19
blocked nose	3.26	2.88	2.41**	1.89**	0.20
watery eyes	2.93	2.37*	1.85**	1.37**	0.23
itchy eyes	3.09	2.50	1.94**	1.62**	0.23
overall symptoms	3.37	2.92	2.04**	1.66**	0.24

Significance of comparison with placebo:
* $p < 0.05$
** $p < 0.01$
Number of patients = 40
_____ indicates treatment means that are not significantly different at the 5% level
acr. = acrivastine
pseud. = pseudoephedrine

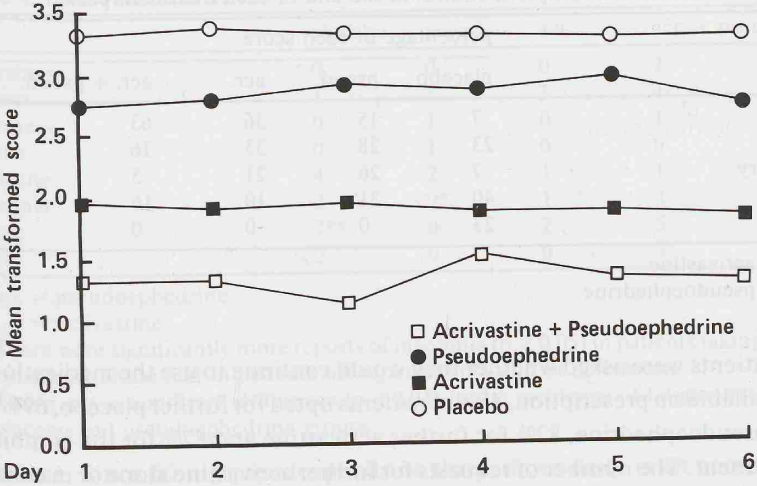

Figure 1. Overall symptoms. Mean daily symptom scores during treatment days 1–6.

symptoms in the following decreasing order: placebo, pseudoephedrine, acrivastine, acrivastine/pseudoephedrine combined.

Both acrivastine alone and in combination were significantly better than either placebo or pseudoephedrine for all symptoms ($p < 0.01$). Acrivastine in combination with pseudoephedrine was significantly better than acrivastine alone in alleviating the symptoms of sneezing, itchy nose/throat, running nose, blocked nose and watery eyes.

The carry over effect of one treatment on the following treatment was tested for each symptom by including pretreatment as a factor in the analysis of variance. No significant carry over effects from one treatment period to the next for any symptom were observed. Analysis of variance was also performed separating the treatment effects into those of acrivastine, pseudoephedrine and their interaction to see if there was a significant antagonistic or synergistic effect in any symptom when using the combination. An additive, rather than synergistic effect was observed when acrivastine and pseudoephedrine were used in combination.

Table 3 gives the percentage of patients and investigators who rated treatment efficacy at the end of each period as excellent, good, satisfactory, poor or abysmal. These results were analysed using the Wilcoxon signed ranks test (Wilcoxon, 1945). There were no significant differences between the patients' and investigator's assessments. Pseudoephedrine was assessed as being significantly better than placebo ($p < 0.01$) and acrivastine alone or in combination were significantly better than placebo or pseudoephedrine alone ($p < 0.01$). The combination treatment produced a lower overall mean assessment score than acrivastine alone but the difference did not reach statistical significance.

Table 3. Assessment of symptom control at the end of each treatment period.

	percentage of each score			
	placebo	pseud.	acr.	acr. + pseud.
excellent	7	15	36	63
good	23	28	33	16
satisfactory	7	26	21	5
poor	40	31	10	16
abysmal	23	0	0	0

acr. = acrivastine
pseud. = pseudoephedrine

When patients were asked whether they would continue to use the medication if it was available on prescription, 45% of patients opted for further placebo, 69% for further pseudoephedrine, 82% for further acrivastine and 87% for the combination treatment. The number of requests for further acrivastine alone or in combination were significantly greater ($p < 0.01$) than for placebo when analysed by the sign-test (Dixon and Mood, 1946).

Adverse experiences

The incidence of adverse experiences, as shown in Table 4, was compared between treatments in pairs using a sign test (Dixon and Mood, 1946). Both acrivastine alone and acrivastine and pseudoephedrine in combination were well tolerated. There was no significant difference in the number of adverse experiences reported in either of these two groups compared to the number of adverse experiences reported in the placebo group. There were significantly more reports of insomnia ($p < 0.05$) in patients taking pseudoephedrine alone (23%) than in patients taking either placebo (5%) or acrivastine (3%). Fatigue was the second most frequently reported adverse experience, being reported twice during acrivastine treatment, five times during the combination therapy and seven times during placebo treatment. No patient taking pseudoephedrine complained of this side effect and the difference in incidence between the placebo and pseudoephedrine groups is significant ($p < 0.01$). Dryness of the mouth, nose and throat was the third most frequently reported adverse experience but there were no significant differences between any of the treatments. There were only two cases of drowsiness which were reported during treatment with the combination; both were considered to be mild.

DISCUSSION

Previous studies have indicated that 8 mg acrivastine three times daily is the optimal dose for alleviating the symptoms of seasonal allergic rhinitis (Gibbs, 1985; Gibbs et al., 1988). The results of this present study confirm the efficacy of

Table 4. Adverse experiences.

	placebo	pseud.	acr.	acr. + pseud.
drowsiness	0	0	0	2
dryness	1	5	3	4
jitteriness	0	1	0	1
nausea	0	1	0	0
headache	4	2	1	1
insomnia	2	9*	1	3
fatigue	7**	0	2	5
other	2	0	0	3

pseud. = pseudoephedrine
acr. = acrivastine
* There were significantly more reports of insomnia ($p < 0.05$) in patients taking pseudoephedrine alone that in patients taking either placebo or acrivastine.
** There was a significant difference ($p < 0.01$) in the incidence of fatigue between the placebo and pseudoephedrine groups.

this dose. Since 60 mg pseudoephedrine three times daily is an accepted oral dosage regime, this dose was selected to be combined with 8 mg acrivastine in the assessment of combination therapy.

A potential problem with a cross-over study design arises from the variation of the pollen count over the treatment period. By randomizing the treatment order, however, this problem was minimized. A washout period of one day was included in the study design. Acrivastine has a half-life of 1.7 hours and following a single dose of 4 mg acrivastine the wheal and flare response to histamine is suppressed up to 7 h 45 min post drug (Cohen et al., 1985b). In view of the relatively short half-life a one day washout was felt to be sufficient, in order to establish a baseline before the start of the next treatment period.

The results of this study have shown, in patients with moderate to severe symptoms of allergic rhinitis, that acrivastine alone or in combination with pseudoephedrine, can significantly reduce the symptom severity scores for sneezing, itchy nose/throat, running nose, blocked nose, watery eyes and itchy eyes relative to placebo or pseudoephedrine. The combination of acrivastine and pseudoephedrine was more effective in alleviating most of the symptoms of hay fever than acrivastine alone and acrivastine, in turn, was more effective than pseudoephedrine. In addition all active treatments were better than placebo.

In the assessment of overall efficacy of treatment at the end of each period, 63% of patients described symptom control as excellent with the combination, compared with 36% for acrivastine alone, 15% for pseudoephedrine alone and 7% for placebo. Both acrivastine alone and in combination were rated significantly better than either placebo or pseudoephedrine but the difference between the two acrivastine periods did not reach significance.

Acrivastine was very well tolerated and associated with few side-effects. The most commonly reported adverse experiences, insomnia and dryness of the

mucous membranes, were associated predominantly with the use of pseudoephedrine. The third most common complaint, fatigue, was reported significantly more during placebo treatment and may have been related to disturbed sleep and a "blocked up" or "heavy-headed" feeling in patients with uncontrolled symptoms of hay fever.

CONCLUSIONS

Acrivastine 8 mg three times daily administered either alone or in combination with 60 mg pseudoephedrine was very well tolerated and highly effective in controlling relatively severe symptoms of seasonal allergic rhinitis. Both treatments containing acrivastine were significantly more effective than placebo or pseudoephedrine for alleviating all symptoms.

The combination of acrivastine and pseudoephedrine was superior to acrivastine alone in controlling the symptoms of sneezing, itchy nose/throat, running nose, blocked nose and watery eyes.

An additive, rather than synergistic effect was observed when acrivastine and pseudoephedrine were used in combination.

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