

Astemizole in the Treatment of Hay Fever

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A double-blind parallel trial of astemizole, pheniramine and placebo was carried out in 51 patients with hay fever. Astemizole is a new potent H₁-antihistamine with long duration of action but devoid of central activity. Evaluation criteria were daily symptom- and side effect score cards, daily nasal peak flow measurements, clinical examination and blood tests. Control of nasal symptoms was significantly better with both antihistamines than with placebo. Tiredness and anticholinergic side effects were less common in the astemizole group than in the pheniramine group. No significant changes in the "safety evaluation" blood tests were observed.

Key words: hay fever; H₁-antihistamines.

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Hay fever symptoms are usually well controlled with H₁ receptor-blocking antihistamines. The adverse reactions elicited by antihistamines, e.g. sedation, insomnia, dryness of the mouth, mostly due to their action on the central nervous system or anticholinergic effects, limit the usefulness of these drugs.

Astemizole is a new H₁ blocking antihistamine with high potency. It has a plasma half-life of over 4 days (4). Studies in animals have shown that it does not cross the blood-brain barrier in amounts sufficient to cause CNS symptoms. Signs indicative of an anticholinergic effect have not been observed with astemizole (5).

The present report describes a study of astemizole in hay fever patients. The purpose of the study was to compare the therapeutic effect and side effects of astemizole with those of pheniramine and placebo. Pheniramine is one of the commonest pure antihistamines with once-daily dosage used in Finland.

PATIENTS AND METHODS

Fifty-one patients, 29 women and 22 men, were included in the study. Their ages varied from 16 to 53 years, and they had had seasonal rhinitis symptoms, caused by birch pollen, on an average for eight seasons (range: 1-34). Their birch pollen allergy had earlier been confirmed by skin testing or by RAST determination. Individual sensitivity to birch pollen was tested by nasal provocation, using serial dilutions from 1:1000 to 1:1 of birch pollen antigen, manufactured by Dome Laboratories, Slough, U.K. (3). The patients were ranked as "very sensitive" when the dilution of 1:1000 or 1:100 was sufficient to elicit a positive reaction, and as "sensitive" when the dilution of 1:10 or 1:1 provoked a positive reaction. At the time of the trial the patients had no other rhinologic or therapy-demanding allergic diseases. They all lived in or near the city of Helsinki.

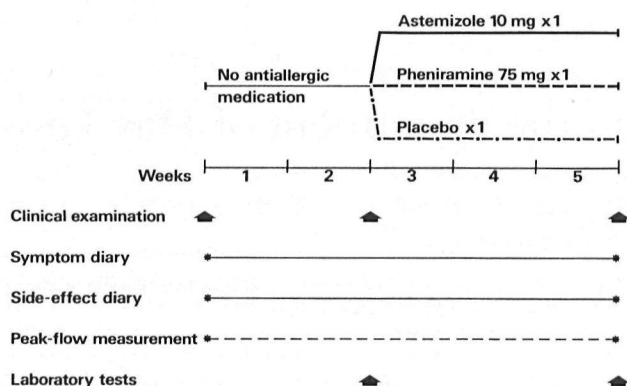


Fig. 1. Plan of the trial showing drug used and examinations performed.

The trial was designed as a double-blind, parallel study (Fig. 1). The patients were randomly assigned to three therapy groups so that "very sensitive" and "sensitive" patients were evenly distributed among the three groups. The test preparation, 10 mg of astemizole (Janssen Pharmaceutica, Belgium), 75 mg of pheniramine (Hoechst, West-Germany), or placebo, was taken in a single dose at bedtime using the "double-dummy" technique. There were 16 patients in the astemizole group, 20 in the pheniramine group, and 15 in the placebo group. The groups did not differ in regard to age and sex distributions.

The evaluation criteria are listed in Fig. 1. The patients completed daily symptom score cards throughout the trial, using a scale of 0–3 for nasal symptoms (running, blockage, itching and sneezing), ocular symptoms (itching, redness, swelling) and dyspnoea. Untoward effects (tiredness, insomnia, dryness of the mouth, palpitation, headache and other possible side effects) were evaluated according to the same scale.

The first 22 patients (5 in astemizole group, 8 in the pheniramine group and 9 in the placebo group) measured their nasal peak flow at bedtime and on getting up in the morning, recording the highest of three measurements.

The patients were provided with additional medication, i.e. tablets containing 6 mg of brompheniramine and 75 mg of phenylpropanolamine, to be taken in case of severe symptoms.

Tablet consumption was recorded in the diary. Laboratory tests to evaluate the safety of the therapy (SR, Hb, leuc. diff. count, thrombocyte count, GOT, GPT, creat.) were performed at the beginning and at the end of the trial.

Fig. 2 shows the daily birch pollen count in Helsinki during the trial weeks. Weeks 1 (no birch pollen), 3 and 4 (high pollen count at both weeks) were taken into account in the statistical analyses. The following statistical methods were used: Friedman's variance analysis to evaluate changes within groups, the Kruskal-Wallis test to analyse differences between groups, the Student's *t* test for peak flow results, and the chi-square test for three independent samples (except when the expected value was less than five in any of the cells).

RESULTS

Four patients failed to complete the trial. Three patients in the placebo group stopped treatment after 6, 9 and 10 days because of fatigue or headache, and one patient in the pheniramine group left the Helsinki area. These patients are included in the analyses.

The total nasal symptom scores (i.e. sum of the individual scores) are shown in Fig. 2. There was a significant difference ($P < 0.05$) between the mean weekly symptom scores of the three groups during the first week of birch pollination (study week 3).

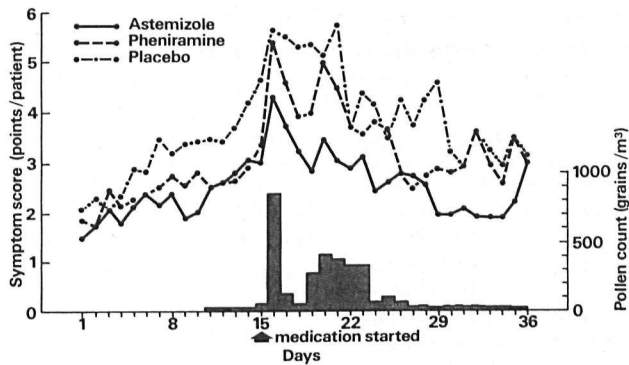


Fig. 2. Daily nasal symptom scores and the concentration of birch pollen grain in Helsinki.

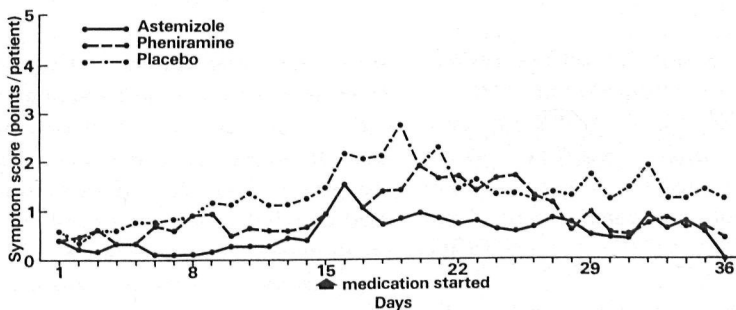


Fig. 3. Daily eye symptom scores.

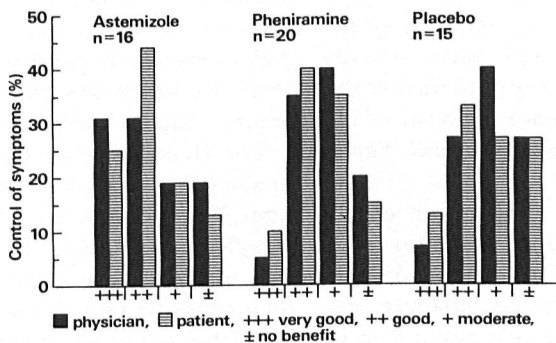


Fig. 4. Physician's and patient's subjective evaluation of the efficacy of the treatment.

Comparison of the run-in period (week 1) and the pollination period (weeks 3–4) showed a significant increase in nasal symptom scores both in the placebo group ($P < 0.001$) and in the pheniramine group ($P < 0.01$). Nasal peak flow results did not reveal significant differ-

ences between either study groups or study weeks.

The total eye symptom scores are depicted in Fig. 3. Ocular symptoms increased significantly in all groups during the pollination weeks (astemizole $P < 0.01$; pheniramine $P < 0.05$;

Table 1

Side effects. Number of patients reporting side effects (patients) and number of days when the side effect was reported (days)

	As		Ph		Pl		χ^2 values	
	Patients (n = 16)	Days (n = 336)	Patients (n = 20)	Days (n = 413)	Patients (n = 15)	Days (n = 277)	Patients	Days
Tiredness	5	11	8	54	5	41	0.33	27.40*
Insomnia	—	—	1	1	1	4		
Palpitations	1	1	—	—	—	—		
Dry mouth	—	—	2	4	2	7		
Headache	4	5	6	14	3	8	0.45	2.71
GI-symptoms	—	—	1	3	—	—		

As = Astemizole group; Ph = pheniramine group; Pl = placebo group.

* $P < 0.001$.

placebo $P < 0.001$), but the differences between the groups were not significant.

Twenty patients (6, 7 and 7 in the respective groups) used additional medication, on an average 1–2 tablets a week. In the pollination weeks, the consumption of tablets increased in the placebo group ($P < 0.05$), but not in the other groups.

The laboratory tests for safety evaluation did not show noticeable changes or differences between the three therapy groups.

According to the patients' and the physician's appraisal of therapy efficacy, relief of symptoms was experienced by more patients in the astemizole and pheniramine groups than in the placebo group. The difference in favour of the active drugs did not reach statistical significance (Fig. 4).

Patients reporting side effects were evenly distributed among the therapy groups. The total number of days when tiredness or dryness of the mouth had occurred was, however, significantly lower in the astemizole group than in the pheniramine and placebo groups. The difference in tiredness was still significant, when only severe or moderately severe side effects (scores of 3 and 2) were included in the calculations (Table 1).

DISCUSSION

In the time period covered by the present trial, birch pollination started abruptly and high pol-

len counts were reached. All testees developed fairly severe nasal symptoms and started medication within the first 2 days of birch pollination. In these circumstances, the grouping of the patients according to sensitivity, as determined by nasal provocation prior to the trial, was of minor importance. However, in the event of a pollen season with low pollen counts, sensitivity assessment may be a useful procedure for obtaining well-matched patient groups for parallel studies of drug efficacy. The shortness of the birch pollen season in Finland makes trials with a cross-over design impractical. The patient groups of the present trial were rather small. Hence, results and statistical calculations require cautious interpretation.

The choice of evaluation criteria and their gradation is always a problem in studies of this kind. The commencement of the pollen season was clearly reflected in the symptom scores and also in the consumption of concomitant additional medication. Thus, these parameters do give information about birch pollen-dependent symptoms, especially if they are evaluated in relation to daily pollen counts. In some earlier studies nasal peak flow measurements have given informative data about nasal blockage (2). The small number of patients using peak flow meters and the concomitant medication, which consisted of a sympathomimetic and antihistamine, may have affected the present results.

According to the parameters employed in this study, astemizole and pheniramine – in that

order – had a better therapeutic effect than placebo. The fact that the daily dose of pheniramine was rather small is probably reflected in the results. It is, however, the dose commonly used in Finland.

In the astemizole group, the number of days when tiredness and headache occurred was smaller than in the control groups. This supports an earlier observation that astemizole would not have CNS effects (1, 5). Dryness of the mouth was rare among the astemizole-treated patients, indicating that the drug does not exert an anticholinergic effect. The absence of the anticholinergic effect did not seem to reduce the effect of the drug on nasal symptoms.

The advantage of antihistamines over intranasal drugs such as sodium cromoglycate and topical steroids is that they relieve not only nasal symptoms but also possible concurrent manifestations of the allergy, e.g. eye or skin symptoms. On the other hand, antihistamines may have sedative effects, strong enough to make them unsuitable for certain patients. In this study, astemizole administered in a dose sufficient to provide relief of symptoms caused tiredness only to a minor degree and it had no anticholinergic effect at all. Individual patient responses to antihistamines often vary considerably, and astemizole must, therefore, be studied in large patient groups before its signif-

icance as an anti-allergic drug can be definitively appraised.

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