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Comparative trial of two non-sedative H_1 antihistamines, terfenadine and astemizole, for hay fever

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ABSTRACT Ninety patients participated in a randomised, double blind, placebo controlled comparison of terfenadine with astemizole in the treatment of hay fever. They entered the trial as a cohort before the grass pollen season and recorded daily their symptoms of itching eyes, sneezing, running nose, and blocked nose on visual analogue scales in diary cards. Over the eight weeks of the trial astemizole was significantly better than either terfenadine or placebo in alleviating itching eyes, sneezing, and running nose ($p < 0.0001$) but no better than placebo for the treatment of blocked nose. The placebo was significantly better than terfenadine for the treatment of running nose and blocked nose ($p < 0.002$). Neither of these H_1 antihistamine drugs was associated with sedative adverse effects despite significantly inhibiting histamine induced skin weal responses. These results suggest that astemizole is a satisfactory non-sedative H_1 antihistamine for maintenance treatment of hay fever. Terfenadine is ineffective by comparison.

Seasonal hay fever is a common complaint affecting at least 10% of the population in Britain[1] at some time in their lives. Many of the symptoms are due to the local release of the inflammatory vasoactive mediator histamine and H_1 antihistamines are widely prescribed for this condition. The beneficial effects of H_1 antihistamines are, however, often offset by their associated anticholinergic and central nervous system sedative effects. Recently two new H_1 antihistamines, terfenadine and astemizole, have been developed that are devoid of both anticholinergic and central sedative actions. This has been confirmed in several clinical trials[2–5] and in detailed psychomotor and visuomotor coordination studies.[6–8] These two H_1 antihistamines differ in that terfenadine is rapidly metabolised and excreted[9] whereas astemizole has a prolonged half life,[10] reflecting its irreversible binding to H_1 receptors and slow release from hepatic lysosomes.[11]

The purpose of this study was to investigate the efficacy of terfenadine and astemizole when compared with placebo in controlling hay fever symptoms.

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Methods

PATIENTS

Ninety patients of both sexes, aged 13–51 years, were entered as a cohort during the week beginning 23 May 1983 and were followed for the subsequent eight weeks. All had positive skinprick test responses to grass pollen and had had classical hay fever symptoms during the previous grass pollen season. Their mean length of history for hay fever was 16·6 (SEM 1·0) years with a range of 1–40 years. Patients were excluded if they had had symptoms consistent with perennial rhinitis, had received a recent course of desensitisation to grass pollen, or were being treated with other H_1 antihistamines, sodium cromoglycate, or corticosteroids.

THE TRIAL

The trial was double blind and placebo controlled. Patients were randomly allocated to receive either terfenadine 60 mg twice a day, astemizole 10 mg in the morning and placebo in the evening, or placebo twice a day. All preparations were administered as identical capsules. Throughout the trial an established oral H_1 antihistamine (clemastine, 1 mg base) was freely available to all patients to be taken, up to twice a day, as additional medication if their symptoms were not adequately controlled.

After starting treatment patients recorded on diary cards each day their symptoms of sneezing, running nose, blocked nose, and itching eyes on separate 10 cm visual analogue scales, marked "absent" to "severe." They were instructed that "absent" indicated no symptoms and that "severe" indicated the worst symptoms that they had experienced at any time. Patients were seen every two weeks throughout the trial and questioned about any adverse effects experienced.

At entry into the trial skinprick tests were performed for response to grass pollen (group B_2 mixed pollens, Bencard) and to histamine acid phosphate (50 μg/ml). These were repeated at the final clinic visit. Skin weal responses were measured, as the mean of two measurements made at right angles, 10 minutes after the skinprick test. Grass pollen counts were performed with a Burkard volumetric spore trap (Burkard Manufacturing Co Ltd, Rickmansworth, Hertfordshire).

The study was approved by the Southampton Ethical Committee and all subjects gave their informed consent.

STATISTICS

Paired and non-paired Student's *t* tests were used to analyse the skinprick test results for grass pollen and histamine within groups and between groups respectively. The daily visual analogue scores for each of the symptoms of sneezing, running nose, blocked nose, and itching eyes from every individual were date matched and differences between treatments over the eight week trial period tested for significance by analysis of variance. The differences in distribution of clemastine use within the three groups were compared by the χ^2 test.

Results

There was no significant difference in the numbers, age, or sex distribution of the patients allocated to the three treatment groups (table). On entry into the trial there was no significant difference between the two active treatment groups with respect to their skin reactivity to grass pollen and histamine (table). The patients who received placebo had a slightly greater response to grass pollen ($p < 0.01$) but not histamine (table). Grass pollen counts were low (<20/m³/24 h) during the first week of the trial and rose to reach a sustained maximum in excess of 800/m³/24 h during June 18–22 then subsequently declined.

During the trial 23 patients sought alternative medication for symptom relief and withdrew from the trial (placebo 9, terfenadine and astemizole 7 each). Two patients also withdrew from the astemizole group because of unrelated illness (tonsillitis and glandular fever). There were no significant differences in the mean number of patient days of treatment between the three treatment groups: terfenadine 48·1 (SD 2·6), astemizole 45·6 (3·0), and placebo 44·9 (2·8) days.

VISUAL ANALOGUE SCORES

The mean daily visual analogue scores for running nose, sneezing, and itching eyes are illustrated in figure 1. Analysis of variance identified astemizole as being significantly better than placebo ($p < 0.0001$) and terfenadine ($p < 0.0001$) in alleviating each of the symptoms of running nose, sneezing and itching eyes. There was no difference between astemizole and placebo in the management of blocked nose, though both astemizole ($p < 0.0001$) and placebo ($p < 0.0001$) were significantly better than terfenadine in the management of this symptom (fig 2). There were no differences in the use of clemastine between the three treatment groups.

SKINPRICK TESTS

In patients receiving astemizole the mean skin weal responses to histamine and grass pollen were reduced after eight weeks' treatment by 97% ($p < 0.001$) and 55% ($p < 0.001$) respectively. The corresponding reductions seen in patients receiving terfenadine were 67% ($p < 0.001$) and 36% ($p < 0.001$) respectively. The reduction associated with astemizole was significantly greater than that seen with terfenadine for both the histamine weal ($p < 0.01$) and the grass pollen weal ($p < 0.01$). The reductions in the histamine and grass pollen weal responses with both H_1 antihistamines were significantly greater than the responses with placebo ($p < 0.001$), which were 15% and 11%.

Numbers, age, sex, and skin reactivity of the patients

Treatment	*No*	*Age (y) (mean (SEM)*	*Sex ratio (M:F)*	*Skin weal (mm) (mean (SEM)*	
				Grass pollen	*Histamine*
Terfenadine	32	29·0 (1·4)	12:20	10·5 (0·5)	4·6 (0·1)
Astemizole	30	30·2 (1·9)	13:17	10·5 (0·5)	4·6 (0·2)
Placebo	28	30·9 (2·0)	14:14	12·8 (0·7)	4·8 (0·1)

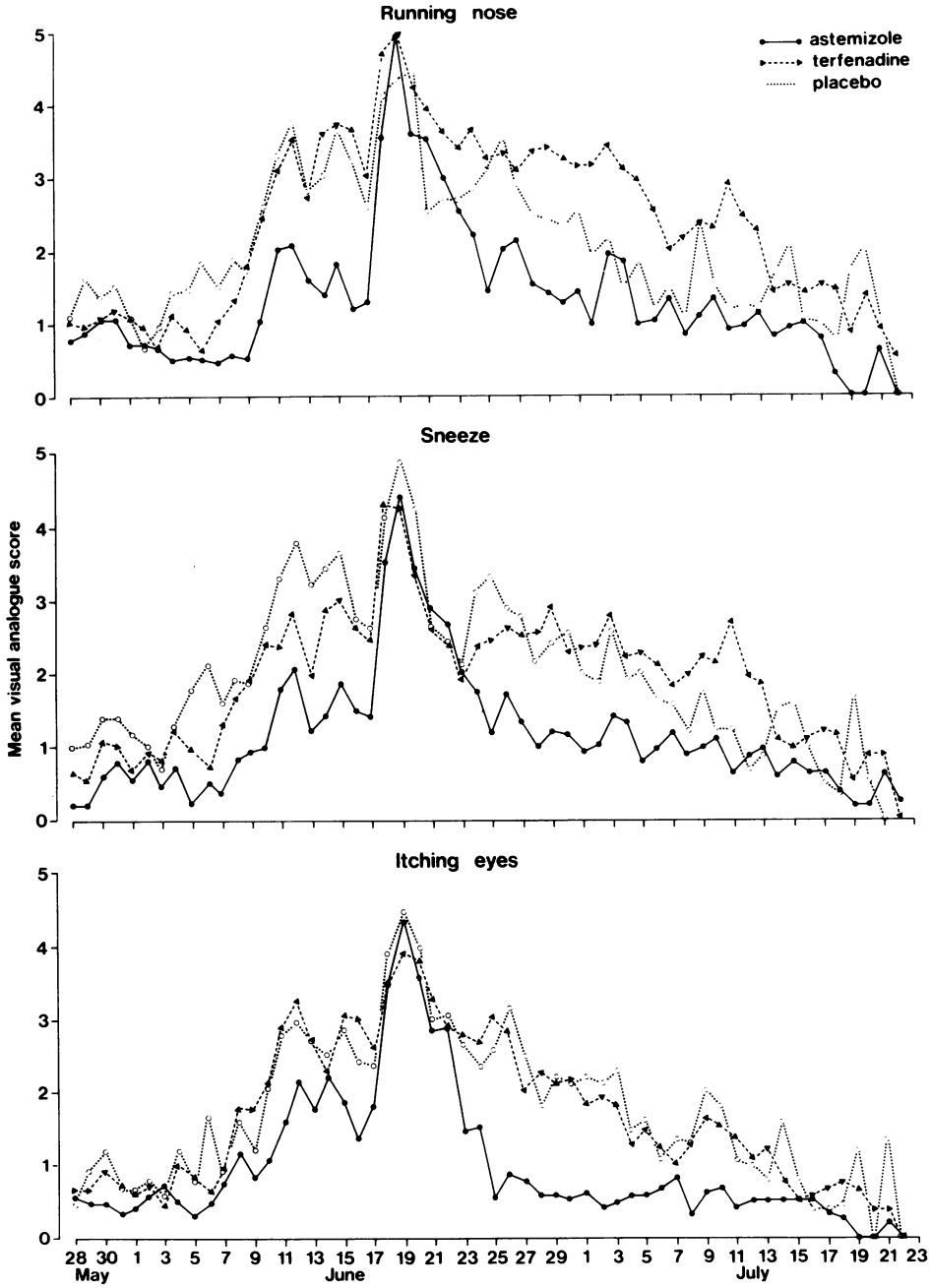

Fig 1 *Date related mean visual analogue scores for running nose, sneeze, and itching eyes for the three treatment groups—astemizole, terfenadine, and placebo.*

SIDE EFFECTS

No difference in the incidence of side effects was identified between the placebo group and those having H_1 antihistamines, a few patients experiencing sedation (placebo 3, terfenadine 0, astemizole 2) or dry mouth (placebo 3, terfenadine 3, astemizole 0).

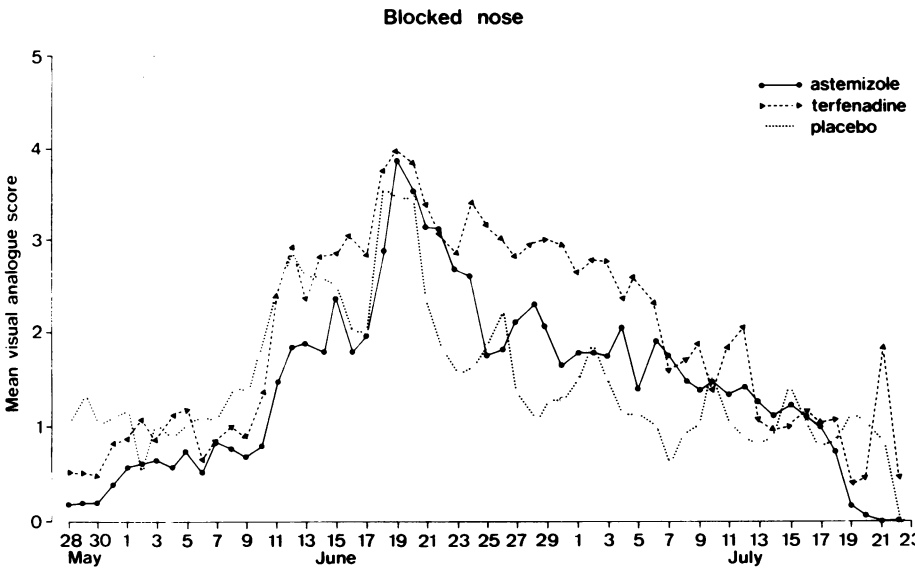

Fig 2 *Date related mean visual analogue scores for blocked nose for the three treatment groups—astemizole, terfenadine and placebo.*

An increase in appetite occurred in two patients receiving astemizole and in one receiving terfenadine.

Discussion

This double blind study shows that, at the recommended clinical dosage, astemizole is a more potent H_1 receptor antagonist than terfenadine and that astemizole is significantly more effective than either terfenadine or placebo for the treatment of running nose, sneezing, and itching eyes (fig 1). The beneficial effects of astemizole compared with placebo for running nose, sneezing, and itching eyes but not blocked nose confirm the results of a previous trial using a less sensitive rating scale scoring system.[5]

By initiating treatment before the grass pollen season it has been possible to assess prevention of the development of hay fever symptoms. This is illustrated in figure 1, which identifies a breakthrough of control between 18 and 22 June coinciding with the peak grass pollen count, which rose to above 800/m³/24 h (concentrations above 150/m³/24 h being associated with symptoms in most patients). The loss of symptomatic control could either be related to reversal of the H_1 receptor antagonism by release of large amounts of histamine into the affected tissues, associated with the high level of antigen exposure, or alternatively to the local release of other inflammatory mediators which produce similar symptoms. The former is unlikely as the binding of astemizole to H_1 receptors is virtually irreversible,[11] significant inhibition of histamine induced skin weal responses being observed for up to 32 days after a single oral dose of 40 mg.[10] In the present study there was 97% inhibition of histamine induced skin weal after eight weeks' treatment with astemizole. Since we have previously shown that peak serum concentrations of astemizole occur within four weeks of initiating treatment and serum concentrations correlate with inhibition of the histamine weal response,[5] maximum H_1 antihistamine activity would have been present at the time of the peak grass pollen count. It is most likely that increased production of other mast cell associated inflammatory mediators, such as leukotrienes, prostaglandins, and kinins, which have been shown to be released from the nasal mucosa after experimental challenge,[12] are responsible for the loss of symptomatic control with high pollen counts.

We were unable to show any significant beneficial effect of terfenadine over that of placebo for the treatment of hay fever. Previous studies of terfenadine have compared it either with placebo or with other H_1 antihistamines, such as chlorpheniramine.[2 3 13 14] Most of these trials were of short duration, lasting only two to nine days, and not all identified significant improvement in symptoms over placebo.[2 14] An explanation for the lack of efficacy of terfenadine when compared with placebo or astemizole in this study cannot be related to bioavailability, as all preparations showed similar dissolution properties, and demonstrable circulating concentrations of terfenadine must have been achieved to produce inhibition of both histamine and grass pollen skin weal responses. The development of tolerance, although recognised with antihistamines,[15] is also unlikely as its profile of protection

compared with that of placebo did not alter throughout the pollen season (fig 1). Little has been published on the pharmacokinetics of long term terfenadine treatment. With single dose studies 99·5% of the absorbed drug undergoes first pass metabolism, being biotransformed into two major metabolites, a carboxylic acid analogue of terfenadine that possesses some H_1 antihistaminic activity and an α-α-diphenyl-4-piperidinemethanol.[9] In view of the extensive metabolism of terfenadine it is possible that its biotransformation may produce a metabolite that interferes with the activity of histamine *N*-methyltransferase or diamine oxidase, enzymes responsible for the metabolism of histamine. Inhibition of histamine *N*-methyltransferase activity is well recognised with some H_1 antihistamines[16] and could account for the failure to gain symptomatic control with this drug despite its 67% inhibition of histamine induced skin weal.

This study confirms previous reports that both astemizole and terfenadine are without significant sedative side effects. It also confirms our previous finding that astemizole is significantly better than placebo for the control of hay fever symptoms, with the exception of blocked nose. In addition, this study identifies that astemizole taken once daily is significantly better than terfenadine for the control of hay fever symptoms. We consider that, in view of its potency and freedom from adverse effects, astemizole is the non-sedative H_1 antihistamine of choice for the maintenance treatment of seasonal allergic rhinitis and conjunctivitis.

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References

[1] Harland RW, McBride NA. Allergic respiratory syndromes in general practice. *Proceedings of British Students' Health Association* 1974:18–23.

[2] Brandon ML, Weiner M. Clinical investigation of terfenadine, a non-sedating antihistamine. *Ann Allergy:* 1980;**44**:71–5.

[3] Backhouse CI, Brewster BS, Lockhart JDF, Maneksha S, Purvis CR, Valle-Jones JC. Terfenadine in allergic rhinitis: a comparative trial of a new anti-histamine versus chlorpheniramine and placebo. *Practitioner* 1982;**226**:347–51.

[4] Wilson JD, Hillas JL. Astemizole: a new long-acting antihistamine in the treatment of seasonal allergic rhinitis. *Clin Allergy* 1982;**12**:131–40.

[5] Howarth PH, Emanual MB, Holgate ST. Astemizole, a potent histamine H_1-receptor antagonist: effect in allergic rhinoconjunctivitis, on antigen and histamine induced skin weal responses, and relationship to serum levels. *Br J Clin Pharmacol* 1984;**18**:1–8.

[6] Nicholson AN, Stone BM. Performance studies with the H_1-histamine receptor antagonists, astemizole and terfenadine. *Br J Clin Pharmacol* 1982;**13**:199–202.

[7] Nicholson AN, Smith PA, Spencer MB. Antihistamines and visual function: studies on dynamic acuity and the pupillary response to light. *Br J Clin Pharmacol* 1982;**14**:683–90.

[8] Seppala T, Savolainen K. Effect of astemizole on human psychomotor performance. *Curr Ther Resp* 1982; **31**:638–44.

[9] Garteiz DA, Hook RH, Walker BJ, Okerholm RA. Pharmacokinetics and biotransformation studies of terfenadine in man. *Arzneim-Forsch/Drug Res* 1982; **32**:1185–90.

[10] Chapman PH, Rawlins MD. A randomised single-blind study of astemizole and chlorpheniramine in normal volunteers. *Br J Clin Pharmacol* 1982;**13**:593P (abstract).

[11] Laduron PM, Janssen PFM, Gommeren W, Leysen JE. In vitro and in vivo binding characteristics of a new long-acting histamine H_1-antagonist, astemizole. *Mol Pharmacol* 1982;**21**:294–300.

[12] Naclerio RM, Meier HL, Kagey-Sobotka A, *et al.* Mediator release after nasal airway challenge with allergen. *Am Rev Respir Dis* 1983;**128**:597–602.

[13] Dugue P, Birnbaum J, Poisson A, Charpin J. Clinical studies with terfenadine in seasonal allergic rhinitis in France. *Arzneim-Forsch/Drug Res* 1982;**32**:1206–8.

[14] Brewster BS. Summary of four UK clinical trials with terfenadine. *Arzeim-Forsch/Drug Res* 1982;**32**: 1213–4.

[15] Dannenberg TB, Feinberg SM. The development of tolerance to antihistamines. A study of the quantative inhibiting capacity of antihistamines on the skin and mucous membrance reaction to histamine and antigens. *J Allergy* 1951;**22**:330–9.

[16] Thithapandha A, Cohn VH. Brain histamine *N*-methyltransferase purification, mechanism of action, and inhibition by drugs. *Biochem Pharmacol* 1978;**27**:263–71.