Terfenadine and placebo compared in the treatment of chronic idiopathic urticaria: a randomised double-blind study

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Terfenadine, a potent and non-sedative antihistamine, was shown to be effective in chronic idiopathic urticaria in a double-blind crossover placebo controlled trial. An oral twice daily 60 mg dose of terfenadine was given and itch and wheal parameters were assessed daily. Despite the overall effectiveness of terfenadine, a variable response was noted which was similar to that shown in previous studies with other antihistamines.

Keywords terfenadine chronic idiopathic urticaria

Introduction

Terfenadine, a butyrophenone derivative, is a potent and specific histamine H_1 -receptor antagonist with peak plasma levels occurring 1–2 h after oral administration. Unlike many traditional antihistamines, it shows little or no evidence of sedative or anticholinergic effects in man (Reinberg *et al.*, 1978; Nicholson & Stone, 1982; Weiner, 1982; Woodward & Munro, 1982).

Inhibition of histamine-induced skin wheals in healthy male volunteers is dose-dependent with, at the dosage of histamine used, total inhibition achieved by terfenadine 60 mg twice daily (Huther *et al.*, 1977). It is known to be effective in the treatment of allergic rhinitis (Dugue *et al.*, 1978) and has recently been shown suppressive in the treatment of chronic idiopathic urticaria (CIU) (Cerio & Lessof, 1984).

CIU has been defined as the occurrence of daily skin whealing over a period of at least 3 months with no detectable cause. It is less common in males than in females and demonstrates a peak incidence in the 20–40-year age group. Therapy with various H_1 -receptor antagonists has previously shown that approximately 50% of patients benefit to varying degrees (Champion *et al.*, 1969). The addition of an H_2 -receptor antagonist may provide further benefit (Monroe *et al.*, 1981).

Methods

Subjects

Twenty-one patients with CIU entered the study. All gave a 3 month or longer history of daily urticaria with individual wheals lasting less than 24 h. There was no history of personal atopy or auto-immune disease, nor of aspirin ingestion. Lactating or pregnant patients were excluded from the study, as was a small number of patients who found the eruption so troublesome that they were unwilling to stop currently successful antihistamine therapy. It was felt that these latter patients would be unlikely to comply with the 2-week placebo period. On entry to the trial the following blood tests were undertaken: full blood count, blood film, differential count, erythrocyte sedimentation rate, urea and electrolytes, and RAST panel for common atopic and food allergens.

Trial design

The study was conducted as a double-blind crossover placebo controlled trial. Patients were requested to withhold current antihistamine therapy for 48 h before starting the trial. Terfenadine was administered as a 60 mg tablet taken with morning and evening meals.

Weeks 1 and 2 — terfenadine/placebo
 Week 3 — wash out period
 (no tablets)
 Weeks 4 and 5 — placebo/terfenadine

All the patients recorded daily scores of degree and duration of itch and number of wheals (Figure 1). Volunteered adverse effects, if present, were also noted. Patients were assessed by one of the medical investigators at the start of the study and the trial method explained. Patients subsequently re-attended for assessment at 1 or 2-week intervals.

Patient diary

Day	Date	Skin itch	Itch duration	Wheal no.	Side effects
1					
2					
3					

Itch and wheal scores

Score	Skin itch	Itch duration	Wheal number
0	none	none	none
1	some itch	< 1 h	1–10
2	severe itch	1–6 h	11–30
3	—	> 6 h	< 30

Figure 1 Patient diary card (first 3 days), and scoring system for itch and wheal recording.

Results

Patients

Fourteen of the 21 entrant patients completed all parts of the trial and returned data sheets suitable for study. This patient group consisted of 11 females and 3 males, with a mean age of 51 years (range 27–77 years) and an average duration of CIU of 3.1 years. The seven patients who did not complete the study failed to comply with trial protocol. Three of these left the study because of intolerable symptoms occurring during the placebo period of treatment. The other four failed to attend for clinician assessment despite repeated attempts at contact.

Treatment response

Summated itch and wheal score comparisons for the placebo and terfenadine effect demonstrated reduced mean scores for terfenadine (Figure 2). Comparison of terfenadine vs placebo for itch and wheal scores independently in individual patients is demonstrated on line gradients

(Figure 3) which show a distinct trend of score reduction in blood itch and wheal during the terfenadine treatment period. These data are significant ($P < 0.05$, Wilcoxon Sum Rank Test). Of the 14 patients, 10 preferred terfenadine to placebo and showed a score reduction of $> 25\%$. Of these 10, three had a terfenadine response with virtually a complete suppression of itch and wheals. In this study both itch and wheal scores in the individual patients were reduced by comparable amounts.

Figure 2 Comparison of combined itch and wheal scores for terfenadine and placebo ($P < 0.05$).

Adverse effects

One patient reported an adverse effect, that of drowsiness, which occurred during the placebo period.

Figure 3 Comparison of individual itch and wheal scores for terfenadine and placebo ($P < 0.05$).

Laboratory data

Haematological, biochemical, and immunological assessments were all normal or negative in our subject group.

Discussion

The results of this study correspond to those of Cerio & Lessof (1984), indicating a positive terfenadine effect in the suppression of CIU. The degree of this effect also appears to be similar to that found with other antihistamines (Champion *et al.*, 1969), although differences in study method make direct comparisons invalid.

It is likely that the term 'CIU' embraces a group of conditions which are clinically indistinguishable yet are mediated in a different

chemical manner. As yet, histamine is the only such mediator to have been found elevated in skin blister fluid of CIU patients (Kaplan *et al.*, 1978; Kaplan 1981). Further investigations are required to determine the nature and role of alternative mediators, to explain the inability of antihistamines to effectively suppress wheals in some patients with this condition.

No adverse effects of any sort were reported for terfenadine by patients in this study; and in particular no mention of sedative or other central adverse effects. These results suggest that terfenadine can be considered an acceptable first line non-sedative antihistamine in the treatment of CIU.

Terfenadine and matched placebo were supplied as scored white tablets by courtesy of Merrell Pharmaceuticals Ltd.

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