

Efficacy of mizolastine, a new antihistamine, compared with placebo in the treatment of chronic idiopathic urticaria

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A two-centre, double-blind, randomized, placebo (P)-controlled, parallel-group study was conducted in the UK to examine the efficacy and safety of mizolastine (M), a new H_1 -receptor antagonist, as a once-daily 10-mg dose in chronic idiopathic urticaria. Fifty-six outpatients (M: $n=28$; P: $n=28$) with a mean age of 38 ± 15 years, a duration of disease of more than 3 years, and symptoms of urticaria at least twice a week in the absence of treatment were recruited. After a single-blind placebo run-in period, patients were allocated to one of two treatment groups and were evaluated after 7 and 28 days. The main characteristics (age, duration of disease, number of urticarial episodes, and total score) of the two groups were comparable at inclusion. Mizolastine was shown to improve the urticaria symptoms: at the end of the study, mizolastine produced a significantly greater decrease in the global symptom score comprising itch, wheals, and erythema (M: 2.1 ± 2.1 vs P: 0.4 ± 2.0 ; $P=0.002$). The patient-rated global discomfort from symptoms measured by visual analog scale was significantly improved with mizolastine (M: 31.4 ± 36.7) compared to placebo (P: 5.4 ± 27.6 ; $P=0.003$), with respectively more M responders (74.1%) than P responders (28.6%; $P=0.001$), a responder being a patient with a $\geq 50\%$ decrease in VAS. Premature dropouts due to lack of efficacy and loss to follow-up mainly occurred at the first evaluation (day 7) and were more often observed in patients in the placebo group ($n=17$) than in the mizolastine group ($n=8$) ($P=0.031$). No serious adverse events were recorded. Somnolence was reported in two mizolastine patients, one of whom discontinued the study. Thus, mizolastine may be considered a new treatment option for the symptoms of chronic urticaria.

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Chronic idiopathic urticaria is a relatively common dermatologic condition characterized by the occurrence of episodic or persistent wheals with or without associated angioedema. It may recur frequently over months or years (1–3). Severe itching can be especially problematic. While histamine H_1 -receptor antagonists are the drugs of choice in the symptomatic relief of this condition (4–6), response to these agents is variable and may be incomplete, with tolerance often developing. However, the clinical usefulness of traditional antihistamines is limited by the sedative and anticholinergic effects associated with their use. Mizolastine is a new, potent, long-acting, highly specific H_1 -histamine receptor antagonist (7). Animal models have shown

that mizolastine also inhibits histamine release from mast cells and inflammatory cell migration induced by antigen challenge in the guinea pig through a mechanism independent of H_1 -receptor blockade (8–10). Mizolastine has been shown to be devoid of sedative effects in animals at antihistamine doses (11), and in healthy volunteers at recommended therapeutic doses (12–14). Comparative pharmacodynamic efficacy on histamine-induced wheal and flare was demonstrated in healthy volunteers when compared to placebo and other antihistamines (15). Mizolastine does not potentiate the detrimental effects of alcohol on performance and/or driving (16, 17) and is devoid of anticholinergic effect (18). Results of previous studies have demonstrated that

once-daily mizolastine therapy is effective in relieving the symptoms of seasonal allergic rhinitis (19). The incidence of sedation associated with mizolastine treatment in these studies was low, comparable to that seen with placebo (19). Since antihistamines, including mizolastine, appear to exert their effects by acting as competitive inhibitors of histamine, administration of these agents could relieve pruritus, a primary symptom of urticaria. Mizolastine, with its lack of sedative and anticholinergic effects and convenient once-daily dosing, would have an obvious advantage over traditional antihistamines in patients suffering from allergic diseases.

Therefore, a randomized, placebo-controlled study of the efficacy and safety of mizolastine (10 mg once daily) in the treatment of chronic idiopathic urticaria was conducted. The results of this study are presented in this paper.

Material and methods

This two-centre, double-blind, randomized, parallel-group, placebo-controlled study was conducted in the UK between August 1991 and 1994 in accordance with the amended Declaration of Helsinki, Tokyo, 1991. It followed European guidelines on good clinical practice, and the applicable national regulations on clinical trials, ethical review, and informed consent.

Included patients of either sex, aged more than 18 years, had to have a documented history of chronic idiopathic urticaria with or without associated angioedema with a duration of at least 6 weeks and a frequency of at least an average of two episodes per week in the absence of treatment. Washout periods were required for astemizole (6 weeks) and systemic corticosteroids (2 weeks). Other antihistamines, ketotifen, topical corticosteroids, sodium cromoglycate, and decongestants were stopped 1 week before inclusion.

The investigator assessed the patients for the presence of the main symptoms of chronic idiopathic urticaria (itch, wheals, erythema), using the 4-point scale (20) for itch (0=not present at all, 1=mild: present but not inconvenient, 2=moderate: inconvenient but not interfering with normal daily activities or disturbing sleep, 3=severe: continuously present and interfering with sleep, normal activities, or both), and for wheals and erythema (0=not present, 1=isolated patches, 2=numerous patches, 3=florid rash).

Each morning, the patient completed a diary to record the number of the urticarial episodes in the previous 24 h, the intensity of itch on a 10-cm visual analogue scale (VAS), the number of wheals, and the intensity of the angioedema (0=absent, 1=light, 2=moderate with some disfigurement and/or

sensation of tension, 3=severe, disfiguring with considerable sensation of tension). Patients assessed also the global severity of their symptoms over the previous 3 days on days 0, 7, and 28 on a 10-cm VAS.

The following categories of ineligible patients were excluded from recruitment: patients with urticaria whose cause was known, women who were pregnant or lactating, premenopausal women who were not surgically sterilized or did not use adequate contraception, patients who operated dangerous machinery or for whom driving was part of their work, patients who could not have understood the purpose of the study or could not have complied with treatment or with the study requirements (e.g., psychiatric patients or alcohol or drug abusers), patients who could not correctly complete the diary, patients with major diseases considered clinically significant by the investigator, and patients with clinically significant abnormal laboratory tests.

At the first assessment, a complete medical history was obtained (visit 1), as well as a detailed allergy assessment. Previous treatments for chronic idiopathic urticaria were recorded. Clinical laboratory tests were performed, including haematology and biochemistry with liver function tests. Patients received single-blind placebo medication for a variable period of 4–10 days. Eligible patients were then allocated to one of the two treatment groups according to the randomization. Treatment consisted of one tablet (10 mg or placebo) per day, taken in the evening at 7 pm for 28 days. All tablets were identical in appearance, ensuring the double-blind nature of the trial. Study medication for 1 week and a daily record card were supplied at visit 2.

Symptoms were scored every day by the patient and recorded on the diary card according to the 4-point scales as above. Two further visits took place on days 7 and 28. At each visit, assessments were conducted as at the initial assessment. Entries on the diary card were checked, and the amount of used study treatment was recorded. The investigator recorded all adverse events graded as mild, moderate, or severe, and the relationship of the adverse events to the test drug was assessed as unlikely or probable. Investigators assessed changes in laboratory values and determined whether they were related to the drug.

At the final assessment, the investigator made a global evaluation of treatment according to the clinical global impression (CGI), assessing therapeutic effect (1=marked to 4=unchanged) and adverse events (1=none to 4=outweighs therapeutic benefit). Three components were then derived: the therapeutic effect, the secondary (adverse) effects, and the therapeutic index, which is the ratio of the first two parameters.

Statistical methods

Sample size. It was estimated that 60 assessable patients, i.e., 30 per group, would be required to detect a difference of 45% between the mizolastine group and the placebo group for the primary efficacy variable (percentage of responder patients based on at least a 50% decrease in score on the VAS) with a two-sided significance level of 0.05 and a power of 0.95. The statistical analysis was performed on an "intention-to-treat-basis", i.e., taking into account each patient's having at least one evaluation after randomized treatment.

Comparability of groups. Differences among treatment groups in demographic and baseline variables were tested by the chi-square test (21) for the categorical variables or the one-way analysis of variance test (22) for the continuous variables. Because of the nonnormality of the data, a nonparametric alternative, the Kruskal-Wallis test (23), was used to compare continuous variables among treatment groups.

Principal criteria. The total score was defined as the sum of scores for itch, wheals, and erythema. The score for each symptom was calculated by visit and by patient according to body region (lower limbs, upper limbs, face, and trunk). Mean scores were rounded off to the nearest whole number. The Kruskal-Wallis test was used to compare treatment groups for the total score. The global discomfort from symptoms in the 3 days preceding a visit, as assessed by the 10-cm VAS, was tested by the Kruskal-Wallis test.

These parameters were analysed with an intergroup comparison for their evaluation day 0 to day end and also day 0 to day 7.

The number of responder patients who had at least a 50% decrease in score on the VAS at day end were identified. Fisher's exact probability test (23) was used to compare the two treatment groups for this variable.

Secondary criteria. Criteria such as the therapeutic effect, therapeutic index, itch, and study dropouts due to inefficacy (including loss to follow-up) were analysed with the relevant statistical tests (the Cochran-Mantel-Haenszel test with ridit scores (24), the Kruskal-Wallis test, and Fisher's exact test).

Safety analysis

Adverse events were described by treatment group and type of emergent event. Weight and haemodynamic parameters were compared between the groups at day 0 and day end by the appropriate

ANOVA. Out-of-range laboratory values were flagged.

Results

A total of 56 patients (mean age: 38 ± 15 years) were enrolled, of whom 28 were allocated to mizolastine and 28 to placebo. One patient in the mizolastine group did not take the drug treatment. There were no significant differences between the two groups in demography and baseline disease characteristics (Table 1). On average, patients had symptoms of chronic idiopathic urticaria for more than 3 years, with a mean weekly number of episodes of 4.7 and a mean duration of 8.3 h. The incidence of associated angioedema was comparable between groups at inclusion. Twenty-one patients (78%) in the mizolastine group and 16 (57%) in the placebo group reported associated angioedema ($P=0.103$). Ninety-three percent of patients had previously received treatment, predominantly antihistamines, for their condition. Concomitant allergic diseases were present in 43%. Hay fever was the most common concomitant disease (27%). Allergic asthma was noted in 12% of patients, and inhaled corticosteroids for its treatment were taken by less than 5% of the patients.

A total of 27 patients completed the study, 18 patients in the mizolastine group and nine in the placebo group. Twenty-two patients discontinued prematurely (five in the mizolastine and 17 in the placebo group) due to lack of efficacy, one patient in the mizolastine group withdrew due to drowsi-

Table 1. Baseline demographic and disease characteristics

	Mizolastine 10 mg <i>n</i> = 28	Placebo <i>n</i> = 28	All <i>n</i> = 28
Age (years) (mean $\pm$ SD)	37 $\pm$ 14	39 $\pm$ 15	38 $\pm$ 15
Male (%)	36	54	45
Female (%)	64	46	55
Duration of CIU* (weeks) (mean $\pm$ SD)	165 $\pm$ 280	190 $\pm$ 230	177 $\pm$ 254
Urticarial episode/week (mean $\pm$ SD)	4.6 $\pm$ 1.9	4.8 $\pm$ 2.1	4.7 $\pm$ 2.0
Duration of episode (h) (mean $\pm$ SD)	8.2 $\pm$ 8.4	8.3 $\pm$ 8.8	8.2 $\pm$ 8.5
Patients (%) having angioedema	78	57	67
Patients (%) having received previous treatment for CIU	93	93	93
Concomitant allergic diseases <i>n</i> (%)			
Hay fever	5 (21)	9 (32)	15 (27)
Perennial allergic rhinitis	0	1 (4)	1 (4)
Asthma	5 (18)	2 (7)	7 (12)
Eczema	1 (4)	0	1 (4)

* CIU: chronic idiopathic urticaria.

ness, two patients in the mizolastine group were lost to follow-up at day 7, one patient in each group was considered uncooperative, and the remaining two patients (one in each group) discontinued for reasons unrelated to the study. Premature dropouts due to lack of efficacy, including loss to follow-up, mainly occurred at the first evaluation (day 7) and were more observed in 61% of patients in the placebo group ($n=17$) than 29% in the mizolastine group ($n=8$ and $P=0.031$). The reasons for premature study discontinuation are summarized in Table 2.

Efficacy assessments

Mizolastine 10 mg was clinically superior to placebo in alleviating symptoms of urticaria for all efficacy criteria (Table 3). Efficacy was demonstrated from day 7 of treatment and was maintained to the end of the study. The decrease in total score of urticaria symptoms (itch, wheals, erythema) was significantly higher in the mizolastine group than in the placebo group at day 7 and day end (respectively, $P=0.003$ and $P=0.002$). The improvement in global discomfort from symptoms over the 3 days before each visit was significantly greater in the mizolastine

group than the placebo at day 7 and day end (respectively, $P=0.0002$ and $P=0.003$).

More than two-thirds (74%) of patients (20/28) who were treated with mizolastine were considered responder patients compared with only 28% (8/28) of placebo patients ($P=0.001$) at the end of the study.

The patient distribution according to itch severity was statistically different between groups at day 7 ($P<0.001$) and day end ($P=0.004$); there were fewer patients in the mizolastine group who reported itch than in the placebo group at day 7 (7 vs 23) and day end (12 vs 24) (Table 4). Improvement in global itch occurred in significantly more mizolastine patients than with placebo at both day 7 (20 vs 7) and day end (19 vs 5) (respectively, $P=0.00012$ and $P=0.0003$).

On the CGI scale, a significant difference in favour of mizolastine compared to placebo at day end was observed for both the therapeutic score and the therapeutic index ($P<0.001$ for both analyses).

Safety assessments

Overall, mizolastine was well tolerated. Of the 56 patients randomized, 55 were assessed in safety analyses. A total of 10 patients reported one or more adverse events during the study: 4/28 (14%) in the placebo group and 6/27 (22%) in the mizolastine group. The most common adverse events, regardless of relationship to the study drugs, were CNS (drowsiness, dizziness, headache) and gastrointestinal disorders (diarrhea, nausea). They were all of mild or moderate severity and had spontan-

Table 2. Study completion and premature discontinuation

	Mizolastine 10 mg $n=28$	Placebo $n=28$
Study completion	18	9
Premature discontinuation		
Lack of efficacy	5	17
Adverse events	1	0
Loss to follow-up	2	6
Other	2	2

Table 3. Improvement in total score and in global discomfort and percentage of responder patients (n) after 7 and 28 days of treatment with mizolastine 10 mg: comparison with placebo

	Mizolastine 10 mg	Placebo	P
Total score of urticaria symptoms			
Baseline	3.5 $\pm$ 1.7 (28)	3.2 $\pm$ 2.4 (28)	NS
Day 7	1.0 $\pm$ 1.7 (26)	2.4 $\pm$ 1.4 (28)	0.0004
Day 28	1.4 $\pm$ 1.8 (27)	2.8 $\pm$ 1.8 (28)	0.006
Baseline - day 7	2.5 $\pm$ 2.3 (26)	0.6 $\pm$ 2.0 (28)	0.003
Baseline - day 28	2.1 $\pm$ 2.1 (27)	0.4 $\pm$ 2.0 (28)	0.002
Global discomfort over 3 days before assessment (VAS)			
Baseline	49.8 $\pm$ 28.1 (28)	50.4 $\pm$ 26.5 (28)	NS
Day 7	10.6 $\pm$ 20.7 (26)	47.0 $\pm$ 31.7 (28)	0.0001
Day 28	17.3 $\pm$ 22.7 (27)	44.9 $\pm$ 33.5 (28)	0.001
Baseline - day 7	37.2 $\pm$ 37.5 (26)	3.3 $\pm$ 24.7 (28)	0.0002
Baseline - day 28	31.4 $\pm$ 36.7 (27)	5.4 $\pm$ 27.6 (28)	0.003
Percentage of responder patients at day 28	74.1 (20)	28.6 (8)	0.001

Table 4. Itch improvement after 7 and 28 days of treatment with mizolastine 10 mg: comparison with placebo (n patients and percentage)

		Mizolastine 10 mg	Placebo	P
Presence of itch				
Baseline	Absent	3 (10.7)	6 (21.4)	NS
	Mild	14 (50.0)	13 (46.4)	
	Moderate	11 (39.3)	8 (28.6)	
	Severe	0	1 (3.6)	
Day 7	Absent	19 (73.1)	5 (17.9)	< 0.0001
	Mild	6 (23.1)	17 (60.9)	
	Moderate	0	6 (21.4)	
	Severe	1 (3.8)	0	
Day 28	Absent	15 (55.6)	4 (14.3)	0.004
	Mild	11 (40.7)	17 (60.7)	
	Moderate	0	6 (21.4)	
	Severe	1 (3.7)	1 (3.6)	
Improvement in itch				
Day 7	Yes	20 (71.4)	7 (25.0)	0.0001
Day 28	Yes	19 (67.9)	5 (17.9)	0.0003

eously resolved by the end of the study. No serious adverse events were reported. Two cases of drowsiness occurred in mizolastine patients, one of whom discontinued treatment. In this patient, drowsiness and dizziness of moderate severity occurred 2 h after the first mizolastine dose and led to study discontinuation after day 8 of treatment.

No noteworthy findings, significant changes, impairments, or major abnormalities were recorded as a result of the physical examinations, evaluation of vital signs, or laboratory tests.

Discussion

This study, which aimed to assess mizolastine 10 mg in patients with chronic idiopathic urticaria, showed that mizolastine was significantly more effective than placebo in relieving the symptoms. Assessments were made by both patient and investigator, using symptom scores as primary efficacy measures. Despite the fact that the clinical meaning of mean symptom scores can be criticized, both assessments demonstrated a significant improvement in favour of mizolastine from day 7 of treatment. Symptom relief was maintained throughout the 28-day treatment period. At the study end point, the decrease in symptoms under active treatment was approximately 50% greater than with placebo, a finding which is consistent with what was previously described with other antihistamine treatments (25–29). The greater effect of mizolastine on the global discomfort from symptoms experienced by the patient over the 3 days before each visit was also consistent with the investigator's evaluation of efficacy. Symptomatic improvement in itching, which is considered to be one of the most annoying symptoms of urticaria, was apparent at the end of the first week in 71% of the mizolastine patients, and remained obvious in the same proportion of patients at the end of treatment. The clear improvement in itching in response to mizolastine 10 mg was comparable to that seen with loratadine (27). Loratadine 10 mg day was also shown to demonstrate a more marked symptom score decrease from baseline of 56% when compared with terfenadine 120 mg day (37%) and with placebo (18%) in 120 patients (30). Finally, patients who had at least a 50% decrease in VAS were significantly more numerous in the mizolastine group (74%) than in the placebo group (27%). The CGI investigator's assessment was as accurate as the patient's assessment in discriminating both treatments, and so was the global assessment at the end of treatment. This seems to justify further the use of assessments by both patient and investigator in this therapeutic condition.

The placebo response rate was not unexpected,

for it is regularly seen in other placebo-controlled urticaria trials. Depending on the type of efficacy assessment used, the placebo response which is most often reported is 10–25% (26, 30, 31) but can be as high as 30–40% (2). The main reason for this is probably the study design: patients were required to have symptoms of a certain severity to be eligible. Although, in this study, patients experienced only 4–5 episodes in the 4–10-day run-in, they probably were included when the disease was at its worst, and thus improved on early days, even on placebo. Thereafter, only the placebo responder patients completed the study, explaining a placebo response of 27% consistent with values in other trials.

Similarly, the dropout rate due to inefficacy was higher in the placebo group (61%) than in the mizolastine group (28%) after 7 days of treatment. This could be explained by the fact that the most severely symptomatic placebo-treated patients could not tolerate placebo for longer than 1 week. Mizolastine was comparable to placebo in the overall incidence of adverse events. Drowsiness was reported in two mizolastine patients, one of whom discontinued the study. This sedation rate (7.4%) was one of the lowest described with other antihistamines in urticaria (5, 6). Indeed, cetirizine was shown to induce sedation in 5–20% of patients at a 10-mg dosage (33); more particularly, sedation was recorded in 22% of patients with chronic idiopathic urticaria (28). The nature, frequency, and severity of the other adverse events were of no particular concern: more specifically, there were no adverse events concerning the cardiovascular system.

The results of this trial confirm that mizolastine 10 mg once daily is effective and safe in chronic idiopathic urticaria. Mizolastine may be considered a new treatment option for the symptoms of chronic idiopathic urticaria.

References

- Cooper KD. Urticaria and angioedema: diagnosis and evaluation. *J Am Acad Dermatol* 1991;25:166–7.
- Mathews KP. The urticarias. Current concepts in pathogenesis and treatment. *Drugs* 1985;30:552–60.
- Ormerod AD. Urticaria. Recognition, causes and treatment. *Drugs* 1994;48(5):717–30.
- Monroe EW. Non-sedating H_1 antihistamines in chronic urticaria. *Ann Allergy* 1993;71:585–91.
- Simons FER. H_1 -receptor antagonists. Comparative tolerability and safety. *Drug Safety* 1994;10(5):350–80.
- Simons FER. The therapeutic index of newer H_1 -receptor antagonists. *Clin Exp Allergy* 1994;24:707–23.
- Rosenzweig P, Thebault JJ, Caplain H, et al. Pharmacodynamics and pharmacokinetics of mizolastine (SL85.0324), a new non-sedative H_1 antihistamine. *Ann Allergy* 1992;69(2):135–9.
- Arbilla S, Shoemaker H, Scatton B, et al. SL85.0324, a novel benzimidazole derivative with selective histamine H_1 -

- receptor antagonist properties. *Eur J Pharmacol* 1990;183:222.
9. Lloyd KG, Levrier J, Duval D, Prouteau M, Berry C, Scatton B. Anti-anaphylactic activity of the non-sedative histamine H_1 -receptor antagonist SL85.0324 in the rat and guinea-pig. *Eur J Pharmacol* 1990;183:218.
10. Scatton B, Arbilla S, Allen J, Dana C, Benavides J. Pharmacological properties and autoradiographic distribution of the binding of 3H-SL85.0324, a non-sedative H_1 -receptor antagonist, in the guinea-pig brain. *Eur J Pharmacol* 1990;183:179-30.
11. Depoortere H, Decobert M, Granger P, Riou-Merle F. Pharmacology profile of SL85.0324, a new H_1 -receptor antagonist. *Eur J Pharmacol* 1990;183:1730.
12. Kerr JS, Dunmore C, Hindmarch I. The psychomotor and cognitive effects of a new antihistamine, mizolastine, compared to terfenadine, triprolidine and placebo in healthy volunteers. *Eur J Clin Pharmacol* 1994;47:331-5.
13. Patat A, Gram LF, Dubruc C, Brohier S, Cabanis MJ, Rosenzweig P. Effects of mizolastine, a new antihistamine, on psychomotor performance and memory in elderly subjects. *Int Clin Psychopharmacol* 1994;9:101-8.
14. Patat A, Perault MC, Vandel B, Ulliac N, Zieleniuk I, Rosenzweig P. Lack of interaction between a new antihistamine, mizolastine, and lorazepam on psychomotor performance and memory in healthy volunteers. *Br J Clin Pharmacol* 1995;39(1):31-8.
15. Rosenzweig P, Caplain H, Cabanis MJ, Brohier S, Thebault JJ. Comparative wheal and flare study of mizolastine versus terfenadine, cetirizine, loratadine and placebo in healthy volunteers. *Br J Clin Pharmacol* 1995;40:459-65.
16. Patat A, Stubbs D, Dunmore C, et al. Lack of interaction between two antihistamines, mizolastine and cetirizine, and ethanol on psychomotor and driving performance in healthy subjects. *Eur J Clin Pharmacol* 1995;48:143-50.
17. Vuurman P, Rosenzweig P, O'Hanlon JF. Mizolastine's effects on psychomotor and actual driving performance in healthy volunteers after single 5, 10, 20 and 40 mg doses versus clemastine 2 mg and placebo. *Eur J Allergy Clin Immunol* 1993;48(16):30.
18. Danjou P, Molinier P, Berlin I, Patat A, Rosensweig P, Morselli PL. Assessment of the anticholinergic effect of the new antihistamine mizolastine in healthy subjects. *Br J Clin Pharmacol* 1992;34:328-31.
19. Stern MA, Dunmore C, Theron M. A double-blind comparative study of mizolastine (SL85.0324) 10 mg and placebo in the treatment of seasonal allergic rhinoconjunctivitis in adult patients. *Eur J Allergy Clin Immunol* 1992;47(12):177.
20. Mathews KP. Urticaria and angioedema. *J Allergy Clin Immunol* 1983;72:1.
21. Fleiss JL. Statistical methods for rates and proportions. 2nd ed. New York: Wiley, 1981.
22. Snedecor GW, Cochran WG. Statistical methods. 6th ed. Ames, IA: Iowa State University Press, 1967.
23. Armitage P, Berry G. Statistical methods in medical research. 2nd ed. Oxford: Blackwell Scientific, 1987.
24. Landis JR, Heyman ER, Koch GG. Average partial association in three-way contingency tables: a review and discussion of alternative tests. *Int Stat Rev* 1978;46:237-54.
25. Alomar A, De la Cuadra J, Fernandez J. Cetirizine vs astemizole in the treatment of chronic idiopathic urticaria. *J Int Med Res* 1990;18:358-65.
26. Fox RW, Lockey RF, Bukantz SC, Serbouzek D. The treatment of mild to severe chronic idiopathic urticaria with astemizole: double-blind and open trials. *J Allergy Clin Immunol* 1986;78(6):1159-66.
27. Hamerlinck FFV, Boyden B, Oei HD, et al. A double-blind comparative study of loratadine and astemizole in chronic idiopathic urticaria. *J Dermatol Treatment* 1994;5:199-202.
28. Kalivas J, Breneman D, Thorp M, Bruce S, Bigby M. Urticaria: clinical efficacy of cetirizine in comparison with hydroxyzine and placebo. *J Allergy Clin Immunol* 1990;86:1014-18.
29. Kietzmann H, Macher E. Comparison of cetirizine and terfenadine in the treatment of chronic idiopathic urticaria. *Ann Allergy* 1990;65:498-500.
30. Belaich S, Bruttman G, De Greef H, et al. Comparative effects of loratadine and terfenadine in the treatment of chronic idiopathic urticaria. *Ann Allergy* 1990;64:191-4.
31. Bernstein IL, Bernstein DI. Efficacy and safety of astemizole, a long acting and non-sedating H_1 antagonist for the treatment of chronic idiopathic urticaria. *J Allergy Clin Immunol* 1986;77(1):37-42.
32. Connell JT. Methods of studying antihistamines. *N Engl Reg Allergy Proc* 1986;7(4):346-55.
33. Spencer CM, Faulds D, Peters DH. Cetirizine: a reappraisal of its pharmacological properties and therapeutic use in selected allergic disorders. *Drugs* 1993;46(6):1055-80.

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