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Research Article

Double-Blind, Parallel, Randomized Pilot Study Comparing the Efficacy and Tolerance of Cetirizine 10 mg, Mequitazine 2 × 5 mg and Placebo in the Treatment of Patients Suffering from Chronic Urticaria: Comparison of Suppressive Effects on Histamine-Induced Weals and Flares

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Strategy, Management and Health Policy				
Venture Capital Enabling Technology	Preclinical Research	Preclinical Development Toxicology, Formulation Drug Delivery, Pharmacokinetics	Clinical Development Phases I-III Regulatory, Quality, Manufacturing	Postmarketing Phase IV

In a double-blind, randomized, parallel-group study, 29 adult patients suffering from chronic urticaria were treated with either cetirizine 10 mg od (n = 10), mequitazine 5 mg bid (n = 10), or placebo (n = 9) for 3 weeks.

Three symptoms (weals, erythema, pruritus) were rated according to severity (none, mild, moderate, severe) by the investigator at each of the four visits (days 1, 3, 14, 21). At each visit the investigator and patients also assessed the patients' general condition using a 5-point scoring system (very bad, bad, moderate, good, very good). On day 21 the global evaluation of efficacy and tolerance was assessed by the investigator and patients on a 4-point scale (excellent, good, moderate, bad). Also, a histamine skin-prick test was performed on days 3, 14, and 21. Evaluation of safety was based on the frequency of patients reporting adverse events as well as the clinical laboratory results.

The cetirizine, mequitazine, and placebo groups of patients were comparable at inclusion. Overall compliance with the trial schedule was excellent for all groups.

After 3 days of treatment a significant improvement in control of all urticaria symptoms was observed in the cetirizine group. Cetirizine elicited a statistically significant better control of pruritus ($P = 0.006$) and erythema ($P = 0.018$) than mequitazine on day 21. A trend in favor of cetirizine vs. mequitazine was also observed regarding control of weals ($P = 0.114$).

Cetirizine clearly and rapidly improved the general condition of the patient as evaluated by both patients and investigator compared to the baseline results. The differences vs. mequitazine as well as vs. placebo were statistically significant on every visit, starting from day 3.

After three weeks of treatment, the clinical efficacy results in the cetirizine group were rated by both patients and investigator as excellent or good, which was statistically significantly better than the results obtained in the mequitazine and placebo group ($P < 0.05$).

The histamine skin-prick test results revealed a marked difference for the group treated with cetirizine compared to the two other groups in favor of CTZ. On day 3, cetirizine produced a statistically significant suppression of the weals (98%) and flares (74%), compared to 24% and 3%, respectively, by mequitazine. With respect to the tolerance results, no statistically significant differences were observed between the three groups.

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The safety profile was similar for all groups. No serious adverse event has been reported during the present study, nor did the treatments induce any clinically significant abnormal changes in the laboratory tests.

It can be concluded from the present study that the effect of cetirizine was statistically and clinically significantly superior to that of mequitazine. On the other hand, of all parameters studied there were no marked differences between the patients of the mequitazine group and the patients of the placebo group.
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Key words: cetirizine; mequitazine; chronic urticaria

INTRODUCTION

Histamine plays a major role in provoking symptoms during inflammation and allergic disorders. Urticaria, a skin reaction characterized by transient, bothersome itchy wealing of the skin due to dermal edema and erythema, is a disease of allergic or unknown etiology. Most chronic urticarias, severely impeding the quality of life of those affected, are idiopathic and usually unrelated to allergy [Mattews et al., 1983]. However, the cutaneous mast cell and its main mediator, histamine, have been shown to be involved in practically all types of urticaria. Although many new modalities are available for the treatment of the allergic patient, H_1-antihistamines are still the first-choice medication for the majority of patients suffering from chronic (idiopathic) urticaria. The first-generation (classical) H_1-antihistamines are generally effective in controlling the signs and symptoms of urticaria. However, the usefulness of these agents is sometimes limited by undesirable central nervous system (CNS) and anticholinergic side effects. Since 1982, a number of potent, specific, but, above all, nonsedating antihistamines were introduced, the so-called second-generation H_1-receptor antagonists. Besides being substantially less sedating than the classical antihistamines, the latter drugs also have little or no anticholinergic activity and many of them are effective for 12–24 hours after single intake, thereby increasing patient compliance. Their effectiveness in the treatment of acute and chronic urticaria has been established in a large number of comparative and/or placebo-controlled trials [Campoli-Richards et al., 1990; Kalivas et al., 1990; Abu Shareeah, 1992]. There are several to choose from, including cetirizine, loratadine, terfenadine, astemizole, mequitazine, etc., each with its own pharmacokinetics and "antiallergic" properties. Cetirizine, an active metabolite of the first-generation H_1-receptor antagonist, hydroxyzine, is rapidly absorbed after oral administration, reaches plasma peak levels within 1 h and has a mean elimination half-life of about 9 to 11 h [Campoli-Richards et al., 1990]. Metabolism of cetirizine is minimal and elimination is almost entirely via the kidney. Cetirizine is a very potent [Rihoux et al., 1990; Simons et al., 1990] and highly specific [Snyder & Snowman, 1987] H_1-blocker and, in addition, has interesting antiallergic properties in vivo, particularly in the skin, i.e., inhibitory effect on eosinophil migration during the late-phase allergic response [Fadel et al., 1987; Michel et al., 1986]. Moreover, cetirizine has an inhibitory effect on the late appearance of histamine (skin chamber) [Michel et al., 1988]. Plasma concentrations for mequitazine peak at about 6 h after ingestion and it is cleared from the body, after extensive metabolization, about 38 h after oral intake [Brandon et al., 1985]. In addition to blocking H_1-receptors, mequitazine also inhibits in vivo (skin blister model) histamine secretion in healthy subjects, probably by stabilizing the mast cell membrane [Revuz et al., 1989]. Of the wide choice of newer non-sedating H_1-antagonists, we have chosen to compare in the present study the efficacy and tolerance of mequitazine (one of the first discovered of this class) with cetirizine (a potent H_1-blocker with marked antiallergic effects in vivo), since neither clinical (urticaria) nor pharmacological (histamine-induced weal and flare test) comparisons between these two drugs in patients with chronic urticaria was found in the literature.

PATIENTS AND METHODS

This was a double-blind, randomized, parallel-group study in which the patients of the first group received cetirizine, 10 mg od (manufacturer's recommended dose), patients of the second group, mequitazine 5 mg bid (manufacturer's recommended dose), and patients of the third group received placebo for 21 days. This trial was conducted in accordance with the amended Declaration of Helsinki, Tokyo, 1991. It followed European guidelines on GCP and the applicable national regulations on clinical trials, ethical review, and informed consent.

Patients

Patients eligible for the study were between 15 and 50 years of age, of either gender, willing to give written informed consent, considered reliable and mentally capable of adhering to the protocol, suffering from chronic

urticaria (three attacks per week for at least 6 weeks), and presenting a total score equal to or superior to 6 in the three symptoms assessed (weal, erythema, pruritus).

Excluded from the study were sexually active women of child-bearing age not practicing a medically accepted contraceptive method and pregnant or lactating women, patients with a concomitant chronic disease such as diabetes, asthma, epilepsy, etc., patients previously enrolled in the same trial, patients having participated in another drug trial within the previous three months, patients suffering from renal or hepatic insufficiency or cardiac dysfunction, patients with a hypersensitivity to antihistaminics, cetirizine and mequitazine included, or with a known allergy to lactose, corn-starch, or cellulose, corticosteroid-dependent patients, patients with a large Quincke edema, and patients suffering from alcohol or drug addiction. A washout period was required if patients had been taking drugs that interfered with skin reactivity: 7 days for antihistamines, 14 days for ketotifen, 6 weeks for astemizole, 2 days for anticholinergic agents and $beta_2$-agonists, 1 month for any systemic treatment with corticosteroids, and 1 week for topical corticosteroids.

Study Design

Eligible patients were allocated to treatment with cetirizine, mequitazine, or placebo according to a computer-generated block randomization. Study medication was administered at about 08.00 and 20.00 h. Products were given as identical capsules bid, with placebo as the morning intake in the cetirizine sequence to maintain double-blind conditions.

The study involved four patient visits: an initial visit for evaluation and screening, obtaining consent, and initiation of treatment. Review visits took place after 3, 14, and again after 21 days of treatment at the end of the study.

Evaluation of clinical efficacy and tolerance

The investigator recorded the severity of each symptom (weals, erythema, pruritus) at each visit on a 4-point scale ranging from 0 to 3 (0 = absent, 1 = mild: present but not disturbing, 2 = moderate: disturbing, 3 = severe: symptoms sufficient to limit activity or sleep).

The investigators and patients also assessed the patients' general condition on a 5-point scale (1 = very bad, 2 = bad, 3 = moderate, 4 = good, 5 = very good) at each of the four visits.

At the final visit, the investigator and patients made an overall assessment of the efficacy and tolerance of the treatment using a 4-point scoring system ranging from 1 = excellent, 2 = good, 3 = moderate, to 4 = bad.

Evaluation of pharmacological efficacy

The peripheral H_1-blocking effect was tested by measuring skin reactivity to histamine. The skin-prick test was employed using a histamine dihydrochloride solution in saline (100 mg/ml). These tests were performed in a third-party-blinded manner on the volar surface of the patients' forearms with a Phazet® uncoated sterile lancet. The same skin sites were used at the same time of day at baseline (day 1), day 3, and day 21. Weal and flare circumferences were traced 10 min after challenge with a felt-tipped pen and transferred to transparent paper by the same investigator. From this paper, the areas were objectively measured by one person using a previously described computer system by Rihoux and Dupont [1987]. Each area was measured three times. The final value was the mean of these three values, provided the coefficient of variation was lower than 5%. The values were expressed in square millimetres (means ± SE).

Evaluation of safety

At each visit, including visit 1, the investigator collected possible unusual sensations or adverse events. This was based on his own impression and observations and the subjects' answer to the question: "Do you or did you experience any unusual sensation?"

Moreover, routine hematological and biological laboratory tests were performed before and at the end of treatment, including full blood counts with differential counts and sedimentation rate and biochemistry including serum creatinine, total bilirubin, urea, alkaline phosphatase, aminotransferases (SGOT, SGPT), and tests for albumin and glucose in the urine.

Evaluation of safety was based on the frequency of patients reporting adverse events as well as the clinical laboratory results.

Compliance

Compliance was checked by counting the remaining capsules at the study review visits. Compliance was considered acceptable if capsule counts indicated consumption between 80% and 120% of the prescribed dose.

Statistical Methods

All statistical tests were two-tailed and the level of significance was 5%. For comparison between both groups at onset of the study on the basis of quantitative data, the Kruskal-Wallis test was used. For qualitative data, the coefficient of contingency was used. The evolution of different semi-quantitative parameters was compared between all groups by multivariate analysis of variance for repeated measurements, using differences from baseline values.

RESULTS

A total of 29 patients was enrolled, of whom 10 were treated with cetirizine, 10 with mequitazine, and 9 with

placebo. Two patients were lost to follow-up after visit 2: one placebo patient for ineligibility reasons and one mequitazine patient for unknown reason.

Overall compliance with the trial schedule was excellent for all groups. No concomitant medication was taken (assessed at days 14 and 21).

There were no significant differences ($P > 0.05$) between the three groups in demography and baseline disease characteristics at inclusion, as shown in Table 1. Patients were between 23 and 49 years of age and weighed between 51 and 97 kg. The minimum and maximum height were 160 and 183 cm, respectively.

Evaluation of Clinical Efficacy and Tolerance

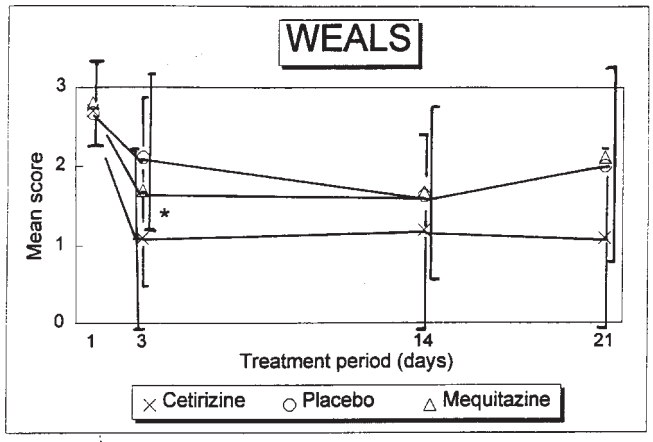
The severity of the symptoms, as assessed at baseline, was not significantly different among the three groups with respect to the three mean individual symptom scores (see Table 1). Cetirizine elicited a statistically significant better control of pruritus ($P = 0.006$) and erythema ($P = 0.018$) than mequitazine on day 21. A trend in favor of cetirizine vs. mequitazine was observed regarding control of weals ($P = 0.114$), as shown in Figure 1. After three days of treatment, a significant improvement in control of all urticaria symptoms was observed in the cetirizine group of patients: for weals, $P = 0.043$; for pruritus and erythema, $P = 0.07$ (trend). A further improvement was recorded after 14 and 21 days of treatment (Fig. 1). However, a difference between the mequitazine and placebo group was not observed.

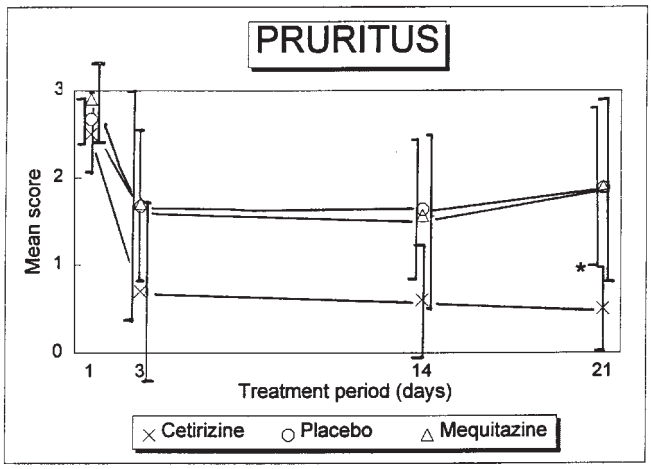
Cetirizine clearly and rapidly improved the general condition of the patient compared to the initial visit results, as shown in Figure 2. The differences vs. mequitazine as well as vs. placebo were statistically significant on every visit, starting from day 3. On the other hand, no significant differences were observed between the mequitazine and placebo groups of patients.

TABLE 1. Demographic Characteristics and Baseline Clinical Evaluation Scores

	Cetirizine	Mequitazine	Placebo
Group size (n)	10	10	9
Age (years)(mean ±sd)	37.7 ± 7.7	35.7 ± 7.8	35.4 ± 7.0
Weight (kg) (mean ±sd)	72.6 ± 10.3	80.6 ± 10.6	71.9 ± 9.1
Height (mm) (mean ±sd)	169.9 ± 7.6	174.0 ± 5.4	170.6 ± 5.8
Sex (n) male	8	9	6
female	2	1	3
Mean (±sd) score for			
weals	2.70 ± 0.48	2.80 ± 0.42	2.67 ± 0.50
pruritus	2.50 ± 0.53	2.90 ± 0.32	2.67 ± 0.50
erythema	2.40 ± 0.52	2.50 ± 0.53	2.33 ± 0.50
general condition (I)	1.80 ± 0.63	1.80 ± 0.63	2.00 ± 0.87
general condition (P)	1.90 ± 0.57	1.70 ± 0.48	2.22 ± 0.67

(I) evaluated by the investigator; (P) evaluated by the patient.
All differences are NS.





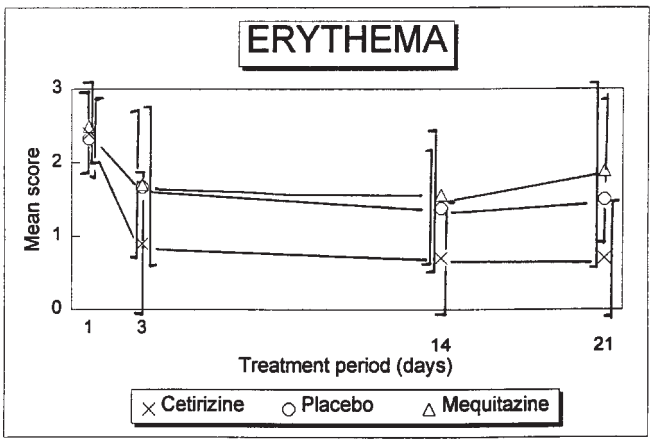


Fig. 1. Evaluation by the investigator at every visit (days 1, 3, 14, and 21). Course of mean score during treatment period for each symptom (weals, pruritus, erythema).
Weals: C vs. M vs. P, $P = 0.2$ // *day 3* C vs. P, $*P = 0.043$.
Pruritus: C vs. M vs. P, $P = 0.01$ // *day 21* C vs. M, $*P = 0.006$; C vs. P, $**P = 0.004$.
Erythema: C vs. M vs. P, $P = 0.05$ // *day 14 C vs. M,* $P = 0.061$ *(trend);* day 21 *C vs. M,* $*P = 0.018$.
Score range: 0 = no symptoms to 3 = severe symptoms.

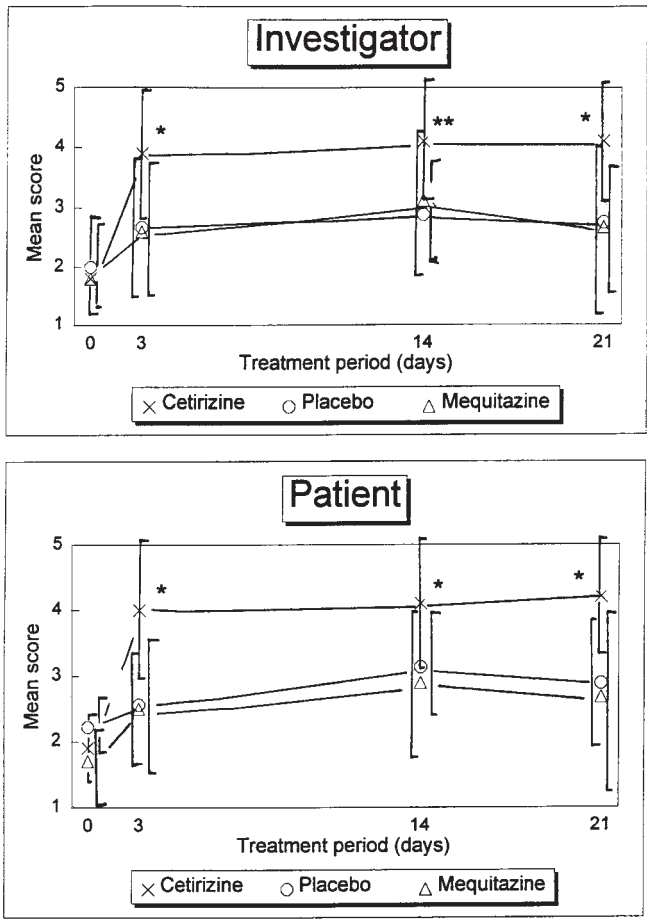


Fig. 2. Evaluation of patients' general condition as assessed by the investigator (I) and the patient (P) at every visit (days 1, 3, 14, and 21). Course of mean score during treatment period.
(I) C vs. M vs. P, $P = 0.004$ // *C vs. M: *day 3*, $P = 0.019$; *day 14*, $P = 0.025$; *day 21*, $P = 0.009$.
*C vs. P: *day 3*, $P = 0.008$; *day 14*, $**P = 0.004$; *day 21*, $P = 0.015$.
(P) C vs. M vs. P, $p = 0.005$ // *C vs. M: *day 3*, $P = 0.014$; *day 14*, $P = 0.067$; *day 21*, $P = 0.026$.
*C vs. P: *day 3*, $**P = 0.0006$; *day 14*, $P = 0.037$; *day 21*, $P = 0.016$.
Score range: 1 = very bad to 5 = very good.

Results of the overall assessment of clinical efficacy and tolerance as evaluated by the investigator and patients are shown in Figure 3. After three weeks of treatment, the mean results in the cetirizine group were rated by both patients and investigator as excellent or good, which was statistically significantly better than the results obtained in the mequitazine and placebo group ($P < 0.05$). Again, there was no marked difference between the mequitazine-treated patients and patients treated with placebo.

Evaluation of Pharmacological Efficacy

The results of the histamine-induced weal and flare tests are given in Table 2. The evolution of weal and flare areas was statistically different from one group to another. The results revealed a marked difference for the group treated with cetirizine compared to the two other groups (mequitazine and placebo). On day 3, cetirizine produced a statistically significant suppression of weals (98%) and flares (74%), whereas mequitazine did not produce a significant inhibition of weals (24%) or flares (3%).

Evaluation of Safety

No serious adverse event was reported in the study. Mild or less than mild drowsiness was noted by four patients on cetirizine, four on mequitazine and by one patient on placebo. One patient on cetirizine complained of a slight headache. Minor changes in the clinical laboratory tests were carefully reviewed — they were minor and considered not to be clinically relevant.

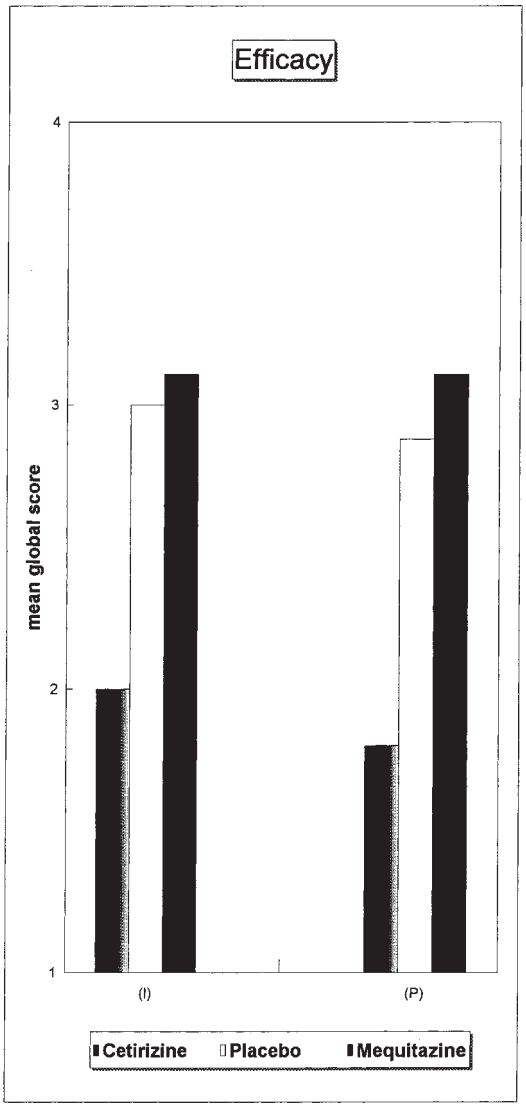
DISCUSSION

The antihistamines are among the most effective agents to suppress urticarial reactions, underlining the pathogenic importance of histamine in this reaction. Many physicians agree that the first-line therapy will be with low-sedating antihistamines, such as both tested agents in the present study.

We have shown in the present study that cetirizine is highly effective in providing patients with symptomatic relief (weals, pruritus, erythema) from urticaria. Consequently, the "quality of life," represented by the patients' general condition results, was significantly improved after only three days of treatment with cetirizine, whereas it was unchanged in the mequitazine group compared to placebo. Also, in a study of six weeks duration with 274 patients suffering from perennial allergic rhinitus, it has been shown that cetirizine was effectively improving "quality of life" (using a SF 36 questionnaire) after a single week of treatment and that this effect was enhanced after six weeks [Bousquet et al., 1996].

These results are in accord with those reported earlier in comparative studies in chronic urticaria, in which cetirizine compares generally most favorably with other non-sedative antihistamines: cetirizine (10 mg od) has consistently been shown to be at least as effective as terfenadine 60 mg bid [Kint et al., 1989] in its effect on the incidence and severity of pruritus, erythema, and weals and to possess some advantages over terfenadine 60 mg bid [Kietzmann et al., 1990] and astemizole 10 mg od [Alomar et al., 1990]. Also, cetirizine is as effective as its widely used predecessor, hydroxyzine, in the treatment of patients with chronic urticaria, with a lower incidence of sedation [Kalivas et al., 1990].

The significantly higher efficacy of cetirizine could be due to a difference in H_1-antihistamine potencies of



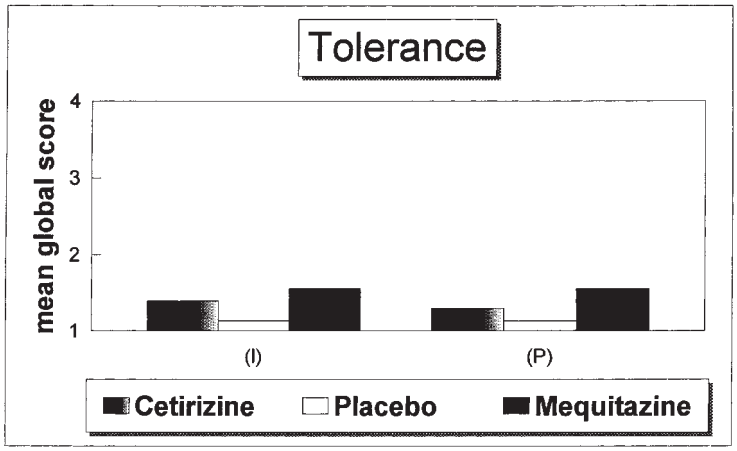


Fig. 3. Global evaluation of clinical efficacy and tolerance as assessed by the investigator (I) and the patient (P) on day 21.
(I) C vs. M. vs. P, $P = 0.05$ // *C vs. M, $P = 0.025$; C vs. P, $P = 0.046$.
(P) C vs. M vs. P, $P = 0.04$ // *C vs. M, $P = 0.017$; C vs. P, $P = 0.047$.
Score range: 1 = excellent to 4 = bad.

TABLE 2. Pharmalogical Evaluation Before and During the Treatment Period

A. Weal Area (mm^2) (mean ±sd)	Day 1	Day 3	Day 21
Cetirizine	137.3 ± 105.4	1.9 ± 5.9*	4.2 ± 7.8**
Mequitazine	77.0 ± 50.0	58.2 ± 44.2	47.1 ± 20.1
Placebo	81.2 ± 30.8	73.4 ± 45.9	147.4 ± 156.4

*Day 3 : C vs. M, $P = 0.0062$; C vs. P, $P = 0.0012$;
**Day 21 : C vs. M, $P = 0.0168$; C vs. P, $P = 0.0004$ // C vs. M vs. P, $P = 0.0006$.

B. Flare Area (mm^2) (mean ±sd)	Day 1	Day 3	Day 21
Cetirizine	1041.5 ± 524.8	270.0 ± 260.5*	210.5 ± 209.2**
Mequitazine	681.3 ± 363.7	662.3 ± 374.4	719.3 ± 356.4
Placebo	890.2 ± 357.8	901.3 ± 477.0	770.8 ± 376.3

*Day 3 : C vs. M, $P = 0.0039$; C vs. P, $P = 0.0336$.
**day 21 : C vs. M, $P = 0.0018$; C vs. P, $P = 0.13$ // C vs. M vs. P, $P = 0.006$.

both drugs. In fact, in the present study cetirizine produced greater and quicker peripheral inhibition than did mequitazine. This confirms the findings in 12 healthy and 12 atopic volunteers of Sidiropoulos et al. [1988], who demonstrated that cetirizine had a more uniform, more pronounced, faster, and longer-acting suppressive effect than mequitazine in suppressing histamine-induced (histamine 0.2 and 2 μg intracutaneously) weal and flare reactions. Moreover, they suggested that cetirizine is possibly the most potent of the new generation of peripheral H_1-receptor antagonists, as did Simons et al. [1990], as well as Juhlin [1995] in his review. It has to be noted also that in the studies below, in which a lower histamine concentration was used than in our study, the results with mequitazine were rather weak, as in the present study. In 24 healthy volunteers, mequitazine was compared with terfenadine, astemizole, and azatadine: the effect of all drugs on the target symptoms after histamine 5 μg differed from placebo, while after 25 μg histamine the weal area was not significantly reduced by mequitazine, whereas there was still a clear effect on erythema [Paul et al., 1989]. All other drugs inhibited weal and flare areas significantly. Histamine skin reactivity (histamine 1 and 10 mg/ml, skin prick) with mequitazine has also been evaluated in 29 healthy subjects. The authors demonstrated that the suppression of weals and flares was significant; however, of weals not clinically relevant [Vichyanond et al., 1991].

Moreover, it could also be explained by additional properties of cetirizine which are relevant to the late-phase allergic response. The late-phase allergic reaction is characterized in part by eosinophil infiltration at the reaction site. This late eosinophil recruitment is associated with the tissue damage and chronicity of the allergic response, as in chronic urticaria. At the skin level, cetirizine has been shown to inhibit recruitment of inflammatory cells, such as eosinophils, neutrophils, and basophils to the site of the allergic reaction [Fadel et al., 1987; Charlesworth et al., 1989] and to inhibit late release of histamine in the skin [Michel et al., 1988].

The absence of the above effects (difference in H_1-antihistamine potency and properties of cetirizine) by mequitazine might explain the superior results obtained by cetirizine, though the mechanism and clinical significance of these effects remain to be clarified. It has indeed been asked on many occasions if these above mentioned characteristics of cetirizine bring definite advantages in clinical situations, such as chronic urticaria. In the present clinical study, in which both pharmacodynamic and clinical efficacy were investigated, the potency of cetirizine in suppressing histamine-induced weal and flare seems to be reflected in its strong, significant activity in the treatment of chronic urticaria. Moreover, cetirizines' efficacy (sometimes at higher doses) has also been shown in physical urticarias, i.e., cold-induced urticaria [Juhlin et al., 1988] and delayed-pressure urticaria [Kontou-Fili et al., 1991], as well as atopic dermatitis [Hannuksela et al., 1993], diseases which generally respond poorly to treatment with antihistamines.

With respect to the tolerance results, no statistically significant differences were observed between the three groups. No serious adverse event was reported during the present study, nor did the treatments induce any clinically relevant abnormal changes in the laboratory tests. Physicians may encounter occasional complaints of sedation with any second-generation H_1-antagonist. However, in comparative clinical trials it appears that the incidence of sedation with cetirizine is similar to that of other nonsedating antihistamines, such as terfenadine and astemizole, and substantially less than that with ketotifen, chlorpheniramine, or mequitazine [Kalivas et al., 1990; Rihoux & Dupont, 1987]. So cetirizine is characterized by a better therapeutic index, i.e., ratio of efficacy to tolerance, than mequitazine.

In this double-blind, multicentric, randomized study, patients suffering from chronic idiopathic urticaria were treated with either cetirizine 10 mg od (n = 10), mequitazine 5 mg bid (n = 10), or placebo (n = 9) for 3 weeks.

It can be concluded from the present study that the effect of cetirizine was statistically and clinically significantly superior to that of mequitazine. On the other hand, of all parameters studied there were no marked differences between the patients of the mequitazine group and the patients of the placebo group.

We have confirmed the value of cetirizine in affording relief of symptoms of urticaria and in particular shown it to be effective and well tolerated, as well as to have a fast onset of action.

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