

Double-blind multicenter study on the efficacy and tolerability of cetirizine compared with oxatomide in chronic idiopathic urticaria in preschool children

Mario La Rosa, MD*; Salvatore Leonardi, MD*; Giuseppe Marchese, MD*; Adriano Corrias, MD†; Giovanni Barberio, MD‡; Nicola Oggiano, MD§; and Ivana Grimaldi, MD¶

Background: There are no studies on the use of cetirizine in children under the age of 6.

Objective: We compared the efficacy and tolerability of cetirizine in patients with idiopathic chronic urticaria to the more widely used antihistamine, oxatomide.

Methods: This double-blind study was performed on 62 patients (38 male and 24 female) with idiopathic chronic urticaria, recruited from four different medical centers of the national territory (Ancona, Cagliari, Catania, and Messina). The children's ages ranged from 2 to 6 years (mean 3.85). The patients were randomly assigned to two treatment groups: one group treated 31 children with cetirizine at a dosage of 5 mg q.d., and a second group treated 31 children for the same amount of time with oxatomide, at a dosage of 25 mg q.d. Sixty-two children began the treatment, but five did not finish the study (three in the cetirizine and two in the oxatomide group). Thus, the clinical study and the statistical evaluation were conducted on 57 children (28 cetirizine and 29 oxatomide). The Student's *t* test was used to compare severity of the illness and changes in the hematochemical tests.

Results: Overall, the effectiveness of the two medications in treating erythema, papules, edema, and itching showed comparable therapeutic activity ($P < 0.001$). Neither medication produced significant side effects.

Conclusions: The results of the present study suggest that cetirizine may represent an effective and safe pharmacologic therapy for chronic urticaria in preschool children. There was no evidence for changes in hematochemical and urinary values, demonstrating the safety and the tolerability of the two antihistamines, even when given to young children.

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INTRODUCTION

Urticaria is a cutaneous disease characterized by discrete areas of swelling of the skin, surrounded by normal

pink-colored tissue, with itching of varying intensity. Acute urticaria is characterized by a sudden onset occurring shortly (typically, within 2 to 4 minutes) after exposure to the causative agent.

In chronic urticaria, the skin eruptions occur in successive progression with itching, and intense symptoms may cause irritability and insomnia. The treatment, for both acute and chronic urticaria, requires recognition and elimination of the causative agents or concurrent factors; when causes are not identified, antihistamines are required to control the liberation of inflammatory mediators responsible for the itching.^{1–8}

Cetirizine, an antihistamine that belongs to the family of piperazine compounds, is normally used to treat allergic rhinitis. The daily dosage in adults is 10 mg^{9,10} while the dosage for children older than 6 years is 5 mg.^{11,12} Because the plasma half-life of the drug is shorter in children (6.5 hours) than in adults (9.5 hours), the early studies of cetirizine in pediatrics used two daily dosages.^{11,13,14} Subsequently, it was demonstrated that 5 mg was equally effective if administered twice daily or in one dosage.^{11, 15–17} Because there are no clinical studies using cetirizine in children under the age of 6, we tested this drug in 2- to 6-year-old children suffering from idiopathic chronic urticaria. As a control we used oxatomide, an antihistamine that belongs to the family of piperazine compounds. Its dosage in children is 0.5 to 1 mg/kg twice daily; in adults its half-life is 25 hours (data on file, Jansen registration material for Italian Health Ministry.)

Thus, our double-blind study investigated the efficacy and tolerability of cetirizine compared with the more widely used antihistamine, oxatomide.

Patients

We studied 62 patients (38 male and 24 female) with idiopathic chronic urticaria, who were recruited from four different medical centers in Italy (Ancona, Cagliari, Catania, and Messina). The children's ages ranged from 2 to 6 years (mean 3.85).

The patients were randomly assigned to two treatment groups: one group of 31 children was treated for 4 weeks with oxatomide, administered at

*Pediatric Department, University of Catania, Catania, Italy.

†Pediatric Department, University of Cagliari, Cagliari, Italy.

‡Pediatric Department, University of Messina, Messina, Italy.

§Pediatric Department, University of Ancona, Ancona, Italy.

¶UCB Laboratories, Pianezza, Torino, Italy.

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a dosage of 25 mg q.d. The second group of 31 children was treated for 4 weeks with cetirizine at a dosage of 5 mg q.d.

Of the 62 children enrolled in the study, five discontinued the treatment early (three in the cetirizine and two in the oxatomide group); therefore, the clinical study and the statistical evaluation were conducted on 57 children, of whom 28 received cetirizine and 29 oxatomide.

All the children's parents were adequately informed about the characteristics of the study and gave their written consent in the presence of a witness.

Patients enrolled had the following entry criteria: they represented both sexes, with ages between 2 and 6 years and a body weight ≥ 11 kg; all patients were treated as outpatients; their chronic urticaria had persisted for at least 6 weeks with at least three instances of recurrence of acute urticaria at separate weekly intervals; and they showed at least three of these four urticaria-related symptoms: itching, erythema, papules, or edema.

Before starting the study, each patient underwent a 4-day pharmacological washout. For those patients treated with ketotifen or corticosteroids, a 2-week washout was required.

The exclusion criteria were hepatic or renal diseases, Quincke edema, active infections, corticosteroid dependence, patients who did not adhere to the washout period, hypersensitivity to piperazine, or allergy to paraben, the pharmaceutical excipient in the preparations.

Design of the Study

The study's goal was to evaluate the clinical efficacy and tolerability of cetirizine when compared with oxatomide in children 2 to 6 years of age with idiopathic chronic urticaria.

For admission to the trial, the seriousness of the urticaria needed to be such that the sum of the scores of four specific symptoms (itching, erythema, papules and edema) would be ≥ 6 . We used the following scale for severity: 0 = absence of symptoms, 1 = slight

symptoms present but not annoying, 2 = moderate symptoms that were annoying but not severe enough to hinder daily activity or sleep, 3 = symptoms severe enough to hinder daily activity or sleep. The study plan included a total of three followup visits: the first appointment occurred at the time of admission; the second appointment occurred 14 days after treatment initiation; the third appointment or final examination occurred after 4 weeks of treatment.

Patients admitted to the study were randomly allocated according to a computer-generated schedule to receive either cetirizine (using 10 drops at morning of placebo and 10 drops of cetirizine at night equal to 5 mg q.d.) or oxatomide (using 10 drops in the morning and 10 drops at night, equal to 25 mg q.d.). Double-blind drug preparations were prepared by UCB Pharma (Torino, Italy) using a randomized computerized list.

For ethical reasons, a double-blind double-dummy controlled study was designed and oxatomide used as reference drug. Among the antihistamines available on the Italian market, it is the only one with a dosage administered twice daily. Further, to maintain the double-blind study, considering the different dosages between oxatomide and cetirizine and the different appearance of the two products, we used two placebos. In fact, the investigators gave each patient four bottles: two contained cetirizine or placebo and two contained oxatomide or placebo.

Patients were instructed not to use other drugs, such as antihistamines different from those under study, systemic or topical corticosteroids, sedatives, anticholinergics, β -sympathomimetics, and antibiotics. During each visit, the investigator evaluated the symptoms.

The parents also expressed their personal evaluation of their children's health, by marking a 100-mm visual analog scale (VAS). One extreme was marked with 0 to represent a totally unsatisfactory condition, and the other extreme, marked with 100, corresponded to a totally satisfactory condi-

tion. The same observer performed this evaluation during all three exams.

At the end of the study, the investigators expressed their evaluations on the overall results of the treatment by using a scale of four levels that corresponded to the following: 0 = lack of result, 1 = satisfactory result, 2 = good result, 3 = optimal result.

During all three examinations, evaluations were performed to determine possible side effects and to measure the tolerability of the treatment. During the first and the last examination, hematochemical and urine tests were performed. The laboratory assessments included complete hemochrome-cytometric (hemoglobin, hematocrit, and RBC), WBC count and differential count, blood platelet count, transaminases, total and fractional bilirubin, blood nitrogen, and glucose.

Statistical Evaluation

Statistical evaluation used the Student's *t* test to measure the severity of the illness and changes in hematochemical tests. The Mann-Whitney test was performed on each symptom and on total symptoms to test the basal homogeneity of the two groups.

To compare the effects on the two groups, the following criteria were examined: analysis of variance and calculation of the range on the VAS; Mann-Whitney test on the total symptoms and on single symptoms; Mann-Whitney test on the total symptoms and on the nonparametric hematologic results; χ^2 test to establish frequency of symptom resolution and to establish the effectiveness of the different clinical judgements; Student's *t* test for the hematologic results and for the hematochemical parametric results.

To verify the variations observed within each group, we used Friedman's test on the single symptoms and on the total symptoms.

RESULTS

The randomization produced two balanced groups with regard to age, height, and sex.

For patients of the same age and height, the differences between the

group treated with cetirizine and the control group treated with oxatamide were low and statistically not significant ($P > 0.05$). With regard to weight, the difference between groups was statistically different ($P < 0.05$); however, from a clinical point of view, these differences were not considered to be important in the analysis.

From their clinical histories, urticaria was diagnosed in children assigned to the cetirizine group, on average 12 months and 35 days before recruitment into this study (range 0.8 month to 41 months and 5 days). In contrast, it was diagnosed 12 months and 15 days before recruitment (range 1 month to 64 months and 4 days) in children assigned to the oxatamide group. There were no statistically significant differences between the two groups when the severities of their symptoms were compared by the Mann-Whitney test.

Before treatment, nearly all the patients (85.5%) had undergone a specific therapy for chronic urticaria in the previous 12 months. This applied to 27 of 31 (87%) in the cetirizine group and 26 of 32 (84%) in the comparison group. To verify the efficacy of the therapy, VAS was used; this allows the patients or parents to express their judgment on the state of illness with the use of a scale measured in mm ranging from 0 (severe illness) to 100 (excellent health).

Using the VAS test, a comparison was made between the two treatment groups by analyzing the differences in their results on days 14 and 28 when compared with day 0. The average values demonstrated a progressive temporal response to treatment, but no substantial differences were observed between the two groups ($P > 0.05$; Fig 1).

The investigator measured the symptoms by summation of the individual scores for each symptom (erythema, papules, itching, and edema) during the three examinations, according to the systematic score ranging from 0 (absent) to 3 (severe symptoms).

Because the inclusion criteria included patients with a symptom score

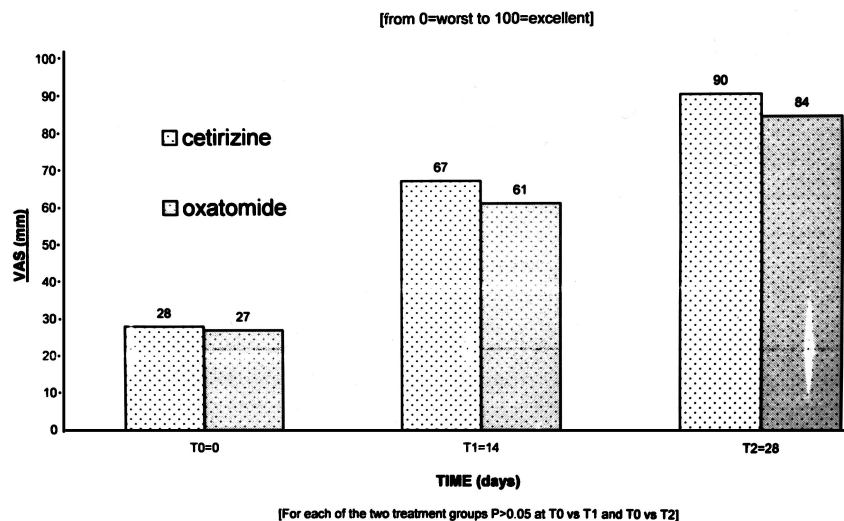


Figure 1. Urticaria symptoms expressed using a VAS. This scale was evaluated by the patients' parents who were asked to express their evaluations on the patients' health (From 0 = worst to 100 = excellent). T0 = beginning of study, T1 = day 14 of study, T2 = day 28 of study. For each of the two treatment groups $P > 0.05$ at T0 vs T1 and T0 vs T2.

of 6, analyses of the final scores of the two treatments were made by comparing the differences of the symptoms at days 14 and 28 with day 0. The average values (Fig 2) demonstrated a progressive reduction in symptoms over time with both treatments. However, the reduction in symptoms was slightly more rapid with cetirizine than with oxatamide.

Statistical analyses for the four symptoms recorded by the investigators are summarized in Table 1. Sixty patients (98%) had erythema at the beginning of the treatment; moderate scores predominated and the groups were not different ($P > 0.05$). During treatment, erythema decreased significantly ($P < 0.01$); by day 28 the sum of the scores decreased by 81.4% in the patients taking cetirizine and by 70.1% in the patients taking oxatamide. Forty-four patients (71%) had papules at the beginning of the treatment; moderate scores predominated and the groups were not different ($P > 0.05$). During treatment, papules and edema (see below) improved more rapidly than the erythema and the itching. By day 14 (T1) patients treated with cetirizine showed a 75% reduction in papule scores; by day 28 they showed

an 85% reduction. In the control group treated with oxatamide, papule scores also improved with a 66% reduction in

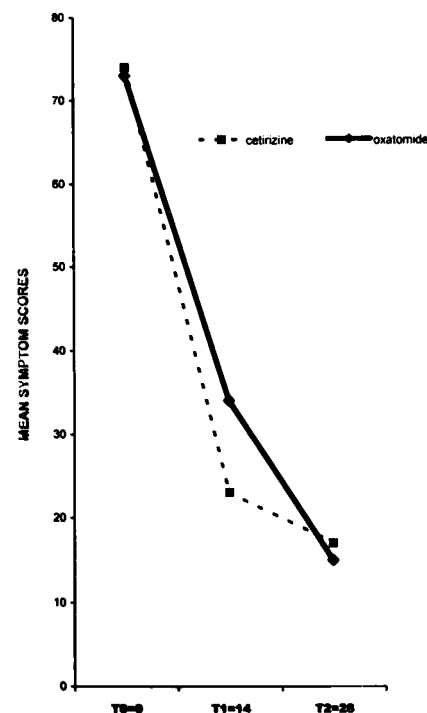


Figure 2. The investigators' mean symptom scores. The symptoms evaluated were itching, erythema, papules, and edema.

Table 1. Mean Scores for Clinical Symptoms at Time Zero and after 14 and 28 Days of Treatment with Cetirizine and Oxatomide

Symptoms	Cetirizine			Oxatomide		
	Time zero (N = 31)	Treatment period		Time zero (N = 31)	Treatment period	
		14 d (N = 30)	28 d (N = 28)		14 d (N = 30)	28 d (N = 29)
Average						
Erythema	1.97	0.80	0.36	2.00	1.07	0.59
Papules	2.00	0.50	0.29	2.00	0.70	0.45
Edema	1.26	0.30	0.00	1.06	0.23	0.07
Itching	2.23	0.67	0.25	2.35	1.27	0.31
Standard deviation						
Erythema	0.48	0.66	0.49	0.45	0.87	0.57
Papules	0.58	0.51	0.53	0.63	0.53	0.57
Edema	0.86	0.60	0.00	0.77	0.50	0.37
Itching	0.50	0.66	0.52	0.49	0.64	0.54
Variation (%)						
Erythema		-58.55	-81.35		-46.50	-70.05
Papules		-75.00	-85.20		-65.52	-78.57
Edema		-76.38	-100.00		-79.09	-93.86
Itching		-69.55	-88.32		-45.49	-86.58
χ^2 *						
Erythema		36.45			31.71	
Papules		38.38			41.95	
Edema		24.50			21.53	
Itching		38.79			47.04	
P		<0.01			<0.01	
U†						
Erythema			466.5		380	322
Papules			479		367.5	342
Edema			426.5		432.5	392
Itching			424		249	382
P			>0.05		>0.05	>0.05
					(<0.001 Itching)	

* Friedman test.

† Mann-Whitney test.

scores by day 14 and 79% reduction by day 28. Therefore, the papule scores improved with both treatments ($P < 0.01$), and the slight improvement for cetirizine was not statistically significant ($P > 0.05$). Forty-three patients (71%) had edema at the beginning of the treatment; moderate scores predominated and the groups were not different ($P > 0.05$). During treatment, 43 patients showed resolution of edema, however, there was no statistical difference between treatments ($P > 0.05$). Forty-three patients (69%) had itching at the beginning of the treatment; moderate scores predominated and the groups were not different ($P > 0.05$). During treatment, itching decreased significantly ($P < 0.01$); by day 28 the sum of the scores decreased by

88% in the patients taking cetirizine and by 87% in the patients taking oxatomide. After 14 days of treatment, patients taking cetirizine reported less itching than did patients taking oxatomide ($P < 0.001$)

The clinical evaluation of the overall effectiveness of the two medications,

given by each investigator on each patient, showed comparable therapeutic activities for the two drugs. Only one child did not benefit from the oxatomide treatment. In contrast, cetirizine demonstrated a slight trend toward more beneficial results, as shown by the higher rate of "excellent" responses in the cetirizine group (33% versus 21% of the comparison group). Overall, the χ^2 score showed no difference between the treatments ($P > 0.05$; Table 2).

The differences between the two groups with regard to the duration of therapy were moderate and statistically not significant ($P > 0.05$). Three of our patients treated with cetirizine and one with oxatomide received dosages of the medication lower than that established by the study.

Cetirizine was used for 26 to 30 days (average: 28.87 ± 0.90), while oxatomide was used for 24 to 33 days (average: 28.14 ± 1.62).

The patients undergoing treatment with cetirizine did not complain of local or systemic undesirable effects. On day 7 of treatment among the group taking oxatomide, one child presented a moderate perioral allergic reaction. This reaction, which was possibly associated with the treatment, caused the parent to stop the child's treatment.

The hematologic, hematochemical, and urinary tests were within the normal limits in all patients before and at the end of the treatment ($P > 0.05$).

DISCUSSION

The rational treatment of urticaria is mainly directed toward the identifica-

Table 2. Clinical Evaluation by Investigators at the End of the Study

Clinical evaluation	Cetirizine		Oxatomide	
	N	%	N	%
Excellent	10	33.3	6	20.7
Good	16	53.3	20	69.0
Moderate	4	13.4	2	6.9
Bad	0	0.0	1	3.4
χ^2			3.1	
P			>0.05	

tion and elimination of all possible causes. Because for many patients this is not possible, antihistamines (anti H₁) are the preferred therapeutic choice. Cetirizine has optimal dynamic pharmaceutical advantages such as selectivity, rapidity of action, relatively short plasma half-life, and fewer side effects on the central nervous system. In addition to its antihistaminic properties, cetirizine also has an inhibitory action on the release of histamine, PAF and PGD₂, as well as on the migration of neutrophils and eosinophils that characterize the secondary, or late, phase of allergic inflammation.^{6,10,17-19}

Cetirizine, a nonsedating antihistamine,^{4-6,9-11,19-25} has been shown to be as effective as terfenadine, hydroxyzine, and chlorpheniramine in reducing the symptoms associated with allergic rhinitis, with asthma induced by pollen and with chronic urticaria. The use of cetirizine in preschool children (under the age of 6 years) with chronic urticaria has not been reported in the international literature. The present study, using one dosage of cetirizine, 5 mg q.d., or oxatamide in two dosages for a total of 25 mg, demonstrated that both drugs were effective in controlling the symptoms of urticaria. In fact, the average values from the three evaluation periods showed that both treatments progressively resolved the symptoms. Cetirizine, however, showed a more rapid resolution of symptoms, as demonstrated by a higher number of resolved cases (46%) in comparison to oxatamide (28%).

Also, for itching, cetirizine was a more effective treatment ($P < 0.01$). Both cetirizine and oxatamide were effective in reducing erythema, papules, and edema symptoms (Table 1; Fig 2).

At the end of the study, the investigators expressed their clinical judgments on the effectiveness of the treatments in each patient. Their judgments were positive for both treatments, although the group taking cetirizine showed more patients with an excellent rating compared with the control group.

Both drugs were well tolerated. No patient in the cetirizine group complained of local or systemic side effects, and only one patient in the oxatamide group presented with a moderate perioral allergic reaction on day 7. This reaction was likely linked to the administration of the medicine. There was no evidence for changes in hematochemical or urinary values of biological relevance, thus demonstrating the safety of both antihistamines, even when given to young children. These results confirm the recent results of a double-blind placebo-controlled trial, called ETAC (Early Treatment Atopic Child), on 817 infants aged 1 to 2 years with atopic dermatitis and with a history of atopic disease in parent or sibling. In this very young population there were no significant differences in the safety profile between the two treatment groups.²⁴

In summary, the present study suggests that cetirizine may represent an effective and safe pharmacologic therapy for chronic urticaria in preschool children.

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- Requests for reprints should be addressed to:*
Dr. Mario La Rosa
Pediatric Department
University of Catania
Via Santa Sofia 78
95123 Catania, Italy
E-mail: mlarosa@mbox.unict.it
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