

Prospective, long-term safety evaluation of the H₁-receptor antagonist cetirizine in very young children with atopic dermatitis

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Background: In very young children, H₁-receptor antagonists have not been adequately studied, although they are widely used and assumed to be safe.

Objective: Our objective was to test the hypothesis that cetirizine would be as safe as placebo for long-term use in this population.

Methods: In the prospective, double-blind, parallel-group, 18-month-long Early Treatment of the Atopic Child (ETAC) study, 817 children with atopic dermatitis who were 12 to 24 months old at study entry were randomized to receive either cetirizine 0.25 mg/kg or placebo twice daily. Safety was assessed by using the reports of all adverse events, diary cards, physical examinations, developmental assessments, electrocardiograms, blood hematology and chemistry tests, and urinalyses.

Results: The population evaluated for safety consisted of 399 children receiving cetirizine and 396 children receiving placebo. Drop-outs and serious events, including hospitalizations, occurred infrequently and were less common in the children receiving cetirizine than in those children receiving placebo, although the differences were not statistically significant. Most reported symptoms and events were mild and were attributed to intercurrent respiratory or gastrointestinal infections, exacerbations of allergic disorders, or age-related concerns rather than to medication-related adverse effects. There were no clinically relevant differences between the groups for neurologic or cardiovascular symptoms or events, growth, behavioral or developmental assessments, laboratory test results, or electrocardiograms, and no child receiving cetirizine therapy had prolongation of the QTc interval.

Conclusions: The safety of cetirizine has been confirmed in this prospective study, the largest and longest randomized, double-blind, placebo-controlled safety investigation of any H₁-antagonist ever conducted in children and the longest prospective safety study of any H₁-antagonist ever conducted in any age group. (*J Allergy Clin Immunol* 1999;104:433-40.)

Key words: Atopic dermatitis, allergy, infant, child, H₁-receptor antagonist, antihistamine, long-term safety, somnolence, QTc interval, randomized trial

Abbreviations used

ETAC: Early Treatment of the Atopic Child

WHO: World Health Organization

In very young children, H₁-receptor antagonists (antihistamines) are widely used for symptom relief in allergic rhinitis, atopic dermatitis, urticaria, and other disorders. They are available in palatable liquid formulations and are assumed to be safe for long-term use when, in fact, no prospective, controlled, comprehensive studies of their safety have ever been published in this age group.^{1,3}

We report the long-term safety of the piperazine H₁-receptor antagonist cetirizine administered in a prospective, double-blind, parallel-group study in which 817 children with atopic dermatitis were randomized to receive either cetirizine or placebo for 18 months. The primary purpose of this study, entitled "Early Treatment of the Atopic Child" (ETAC), conducted in 12 European countries and in Canada from 1994 through 1997 was to ascertain whether cetirizine treatment would prevent or delay the onset of asthma in these high-risk children. Assessment techniques, baseline data, and the efficacy of cetirizine in prevention of asthma and treatment of atopic dermatitis are described in other publications.⁴⁻⁷

METHODS

The protocol for this study was approved by the institutional review boards in each of the participating centers. The children were enrolled between their first and second birthdays after written informed consent was obtained from their parents or guardians. They had atopic dermatitis and at least 1 parent or sibling with a history of atopic dermatitis, allergic rhinitis, or asthma. Exclusion criteria included 1 or more of the following conditions: asthma, any other persistent or recurrent pulmonary disease, other systemic disorders (including neurologic, cardiac, gastrointestinal, developmental, or behavior problems), a history of neonatal distress, sleep apnea (subject or siblings), need for immune-modulating medications or immunotherapy, or adverse reaction to cetirizine, other H₁-antagonists, or parabens. Children with weight below the third percentile for age or with any abnormality of the QTc interval on electrocardiogram were also excluded.

Children were assigned to each treatment group on the basis of a prospective randomization plan. Treatment codes A or B were allocated in blocks of 2, according to a randomization list created with a validated SAS computer software version 6.04 (SAS Institute, Cary, NC). Cetirizine or placebo was assigned to treatment codes independently by the clinical research organization responsible for

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*See Appendix for a complete listing.

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packaging the supplies. At each site, children were given a treatment number in ascending order of their entry into the study.

Cetirizine 10 mg/mL (0.5 mg/drop, 20 drops/mL) or placebo solution similar in appearance and taste but containing no active substance were provided in 20-mL bottles. Cetirizine 0.25 mg/kg or placebo was administered by mouth twice daily with breakfast and the evening meal. Accuracy of dosing was ensured by use of a table of correspondence between body weight, dose, and number of drops per intake.

Symptoms and events

Serious events were reported immediately by the investigator to the sponsor and, where indicated, to regulatory authorities and ethics committees. Throughout the study, the child's primary caregiver recorded all symptoms, illnesses, events, and concomitant medication on a diary card weekly when the child was well and daily when the child was having symptoms. This information was discussed with the investigator by phone as needed and reviewed and entered on the case record forms at the time of the regularly scheduled visits. Before data analysis, the description of the symptom or event was transcribed verbatim from the case record forms and classified according to World Health Organization (WHO) adverse reaction terminology into 30 different system and organ classes. Symptoms or events were more likely to be overreported than underreported for each child for 2 reasons: (1) If several symptoms or events with the same WHO-preferred terminology, but with different dates of onset, were reported; these were counted as different symptoms or events. (2) If symptoms or events involved more than 1 organ system or class, they were counted in each system or class involved. After classification, symptoms and events were reviewed with regard to number, intensity (severity), and relationship to the use of study medication.

Serious events, including hospitalizations, and all other symptoms and events potentially attributable to adverse effects were reviewed by the author in a blinded fashion (ie, without knowing whether the child was receiving cetirizine or placebo).

Objective findings

At baseline and after 1, 3, 6, 9, 12, 15, and 18 months of cetirizine or placebo treatment, history and physical examination (including measurement of height, weight, and vital signs) were performed.

In a subset of children, after 15 to 18 months of treatment, behavior and development were assessed with 2 different instruments. The first instrument, the validated Behavioral Screening Questionnaire, is a semistructured interview during which the parent or caregiver is prompted to describe the frequency, intensity, and duration of 12 different behaviors characteristic of early childhood.⁸ These include attention seeking, eating or sleep disturbances, soiling, concentration, hyperactivity, relationships, temper tantrums, fears, worries, and disobedience. The second instrument, the McCarthy Scales of Children's Abilities for the assessment of psychomotor development in preschoolers aged 2.5 years and older,⁹ was administered to English, French, and Dutch-speaking children; the instrument had been previously validated in these languages.

At baseline and after 1 and 18 months of treatment, or at the time of the last visit in children not completing the study, a 6-lead electrocardiogram (DI, DII, DIII, AVL, AVR, and AVF) was recorded at a paper speed of 50mm/sec. At least 10 QRS complexes (lead DII) were examined for assessment of the QT interval. All electrocardiogram recordings were interpreted by 1 cardiologist who did not know whether a child was receiving cetirizine or placebo. Bazett's correction for heart rate was used.⁷

At baseline and after 3, 12, and 18 months of treatment or at the time of leaving the study, venipuncture was performed for complete

blood count and blood chemistry analysis including alanine transaminase, aspartate transaminase, bilirubin, and creatinine. Complete urinalysis, including glucose, ketones, and proteins, was performed. All blood and urine specimens were analyzed in the laboratory of the Institut Pasteur de Lille, France. If any clinically relevant abnormality was found, the test was repeated as soon as possible and monitored until it returned to a normal value.

Statistical analysis

Computations were performed with the SAS package, version 6.12. Statistical tests were performed 2-tailed at the 5% level of significance. No adjustments for multiplicity were applied. In the analysis of symptoms or events, the number of children with the symptom or event in the cetirizine- or placebo-treated groups was compared by using with the Fisher exact test. Other tests, used where appropriate, included the chi-square test, the Student *t* test, and the Mann-Whitney *U* test. Repeated measures ANOVA was used to analyze the QTc interval over time. Repeated measures analysis of covariance, corrected for age recorded at baseline, was used to evaluate height and weight over time.

RESULTS

Overall safety

The population evaluated for safety consisted of 399 children (61.9% male; mean age, 16.8 ± 4.1 months at study entry) who received cetirizine and 396 children (62.4% male; mean age, 17.2 ± 4.1 months) who received placebo ($P = .121$, *t* test on age). During the 18-month-long study, only 48 children treated with cetirizine and 51 treated with placebo dropped out "for any reason" ($P = .737$, χ^2 test); of these, only 11 and 15 children, respectively, dropped out because of symptoms or events ($P = .421$, χ^2 test). The mean duration of participation in the study was 16.8 months in the cetirizine-treated children and 16.7 months in the placebo-treated children.

Mean compliance with study medication was assessed by measuring the cetirizine or placebo remaining in the 20-mL bottles dispensed at regular intervals throughout the study. Of the bottles dispensed, 60.9% were retrieved. In these, the average compliance was greater than 90% in both the cetirizine- and placebo-treated children. Use of other prescription and nonprescription medications in addition to the assigned study medication did not differ between the cetirizine- and the placebo-treated children, except that significantly fewer children in the cetirizine group were treated with additional oral prescription or nonprescription H₁-antagonists ($P = .047$, χ^2 test).

Serious events were reported in 37 children (9.3%) receiving cetirizine and in 54 children (13.6%) receiving placebo (Table I). The demographics of the children experiencing serious events were similar in the 2 treatment groups, except that the cetirizine-treated children were significantly younger at enrollment than the placebo-treated children (15.3 months vs 17.0 months; $P = .047$, *t* test). Serious events were attributed to study medication in one child receiving cetirizine therapy and 5 children receiving placebo therapy.

Hospitalizations were reported in 36 children receiving cetirizine and in 47 children receiving placebo ($P =$

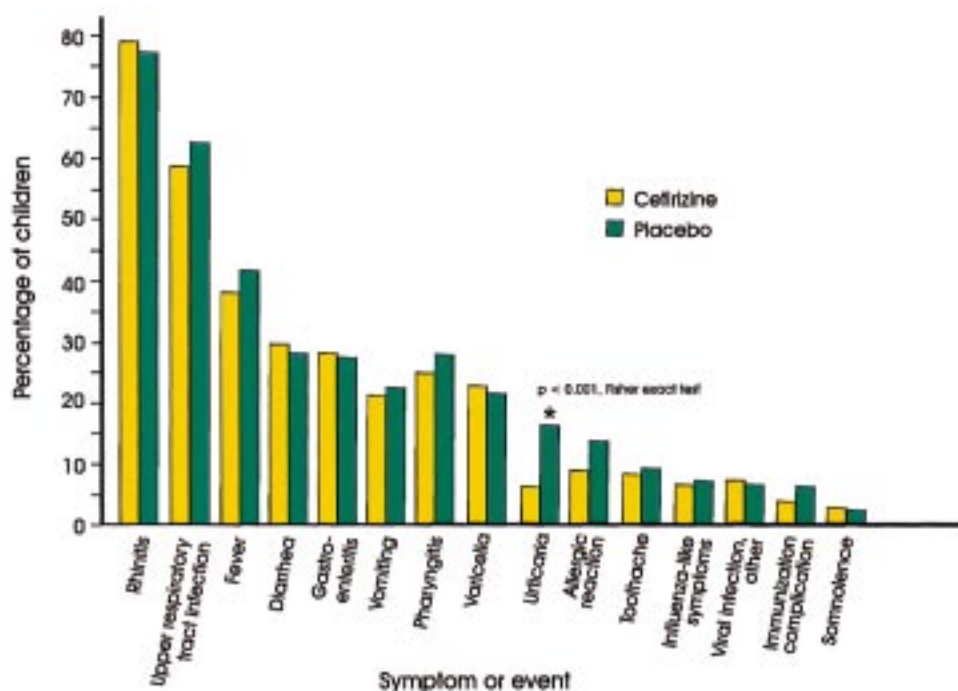


FIG 1. Percentage of children experiencing selected symptoms and events. This information was transcribed verbatim from the case record forms and was classified according to WHO adverse reaction terminology. The most common symptoms and events were related to upper respiratory tract or gastrointestinal tract infections. Less commonly, symptoms and events were related to allergic disorders or to age-related problems, such as toothache (associated with teething) and fever and/or discomfort after immunizations. The cetirizine-treated children had significantly fewer urticaria episodes ($P < .001$) and fewer allergic reactions ($P = .056$); however, apart from this, there were no significant differences between the treatment groups.

.189, χ^2 test), reflecting 39 and 58 events, respectively. Three children receiving cetirizine and 8 children receiving placebo had 2 or more admissions. The most common reasons for hospitalization were infection-related events without asthma (12 children receiving cetirizine and 18 children receiving placebo); asthma with or without infection (8 children receiving cetirizine and 15 children receiving placebo); or injury, surgery, or procedure (8 children receiving cetirizine and 10 children receiving placebo). Ten children (2 children receiving cetirizine and 8 children receiving placebo) experienced an accidental overdose of study medication; however, this led to hospitalization of only one child receiving cetirizine and one child receiving placebo. An 18-month-old boy, who weighed 13 kg, ingested 180 mg cetirizine, confirmed by an extremely elevated urine cetirizine level of 129.0 $\mu\text{g/mL}$, 14 hours after overdose despite ipecac-induced vomiting. He was monitored in the hospital and, apart from a brief period of agitation, had no symptoms. His electrocardiogram remained normal.¹⁰

During the 18-month study, symptoms and events were reported with similar frequency in the cetirizine-treated children and in the placebo-treated children. At least one symptom or event was reported on the diary cards on at least one occasion for most of the children (393 children [98.5%] in the cetirizine-treated group and 391 children [98.7%] in the placebo-treated group). Only

TABLE I. Children with serious symptoms/events

Demographics	Cetirizine	Placebo	P value
Serious symptoms or events/safety population (n)	37/399	54/396	.053
Male/female (n)	28/9	35/19	.270*
Age at baseline (mo)	15.3 $\pm$ 3.3	17.0 $\pm$ 4.3	.047†
Weight at time of event (kg)	8.7-17.6	9.5-19.5	NA
Dose at time of event (mg/kg)	0.23-0.27	0	NA
Days in study at onset of event (n)	13-513	6-565	NA

NA, Not applicable.

*Chi-square test.

†t test.

6 children receiving cetirizine and 5 children receiving placebo were entirely free from symptoms or events. The mean (median) $\pm$ SD number of symptoms or events during treatment was 15.0 (14.0) $\pm$ 9.9 in the cetirizine-treated children and 15.1 (14.0) $\pm$ 9.7 in the placebo-treated children. Most of the symptoms and events were mild and were related to upper respiratory tract or gastrointestinal tract infections, allergic disorders, or age-related concerns, rather than to medication adverse effects (Fig 1). Potential H_1 -antagonist adverse effects such as increased appetite occurred in 2 patients receiving cetirizine and one patient receiving placebo; exces-

TABLE II. No. of children with neurologic symptoms or events*

Neurologic symptom or event	Cetirizine (n)	Placebo (n)	P value (Fisher exact test)
Ataxia (loss of balance)	2	2	1.000
Febrile convulsions	2	4	.450
Fatigue	13	5	.093
Emotional lability	5	6	.772
Hyperkinesia†	5	9	.296
Insomnia‡	35	21	.071
Nervousness§	5	7	.577
Other	5	6	.772
Somnolence	9	8	1.000
Neurologic symptoms or events/total safety population (n)	65/399	55/396	.373

*Symptoms and events, listed alphabetically, did not differ significantly between the treatment groups. In the cetirizine-treated group, 9 children had symptoms and events that were classified as severe versus 8 children in the placebo-treated group. Only 3 children had symptoms or events described as being "related" or "very likely related" to study medication (somnolence in 1 child receiving cetirizine therapy, insomnia in 1 child receiving placebo therapy, and fatigue in 1 child receiving placebo therapy).

†Hyperactivity, hyperkinetic behavior.

‡Trouble falling asleep or restless sleep, sometimes attributed to teething, itching, or intercurrent illness.

§Irritable behavior.

||Hypertonia, hypotonia, tremor, aggression, agitation, absence, headache.

sive thirst was not reported at all. Neurologic symptoms and events are described in detail in Table II. Somnolence was reported with similar frequency in the children receiving cetirizine and in those children receiving placebo ($P = 1.000$). Insomnia was reported more frequently in the children receiving cetirizine than in those children receiving placebo ($P = .071$). Cardiovascular symptoms and events were reported in 4 children receiving cetirizine (a murmur was detected in 3 children, and syncope after an injury occurred in 1 child) and in 6 children receiving placebo (a murmur was detected in 3 children; and tachycardia, other arrhythmia, and extrasystole was detected in 1 child each). None of these events were attributed to study medications.

Mean increases in height and weight during the 18-month study were age appropriate. At baseline, the mean weight of the cetirizine-treated children (10.85 ± 1.46 kg) was significantly less than that of the placebo-treated children (11.07 ± 1.55 kg; $P = .038$, t test). After 18 months of treatment, the mean weights were 14.82 ± 1.89 kg and 14.57 ± 1.87 kg, respectively (Fig 2). When repeated measures analysis of covariance (with age at baseline as the covariate) was performed, there was a significant treatment effect between the baseline weight measurement and the last measurement, evidenced by the interaction between treatment and time ($P < .001$). At the final evaluation, the mean difference in weight between the cetirizine- and placebo-treated children was 250 g.

There were no clinically relevant differences in the mean pulse rate and the mean respiratory rate in the cetirizine- and placebo-treated children at any time.

Behavioral and developmental assessments

Preliminary analysis of Behavioral Screening Questionnaire assessments in 168 children receiving cetirizine and 154 children receiving placebo revealed no significant difference ($P = .604$) between the cetirizine- and placebo-treated children with regard to total scores, which were 6.32 ± 3.13 and 6.51 ± 3.48 , respectively, or with regard to assessment of the 12 behavior subtests. The McCarthy test was administered to 83 children receiving cetirizine and 78 children receiving placebo. There was no significant difference between the cetirizine- and placebo-treated children with regard to mean scores, which were 103.0 ± 14.2 and 103.6 ± 15.3 , respectively. The Behavioral Screening Questionnaire and the McCarthy Scales of Children's Abilities are being repeated at intervals to assess the potential long-term effect of cetirizine administration on the behavior and cognitive development of very young children.

Electrocardiogram results

In all, 2165 electrocardiograms were reviewed. At baseline, 13 electrocardiograms were missing in the cetirizine-treated children, and 9 electrocardiograms were missing in the placebo-treated children. During the study, 49 electrocardiograms were missing in the cetirizine-treated children and 54 electrocardiograms were missing in the placebo-treated children. At the baseline assessment and at the 2 follow-up assessments, all electrocardiograms were within normal limits. The mean corrected QT interval did not differ significantly between the cetirizine- and placebo-treated groups (Fig 3), and no child receiving cetirizine had an increase in the QTc interval.

Eight children receiving cetirizine and 7 children receiving placebo were concurrently taking a macrolide antibiotic, such as erythromycin or clarithromycin, at the time an electrocardiogram was obtained. An additional 14 cetirizine-treated children and 13 placebo-treated children had received a macrolide antibiotic concurrently with study medication during the 2 weeks preceding the electrocardiogram. In these children, the data were scrutinized closely for indirect evidence of possible medication interactions. Coprescription of cetirizine or placebo with macrolide antibiotics did not increase the QTc interval in any child.

Laboratory tests

At baseline and after 3, 12, and 18 months of treatment with study medication, 2925 blood samples were analyzed; only 57 samples were missing. There were no clinically relevant differences in hematology and biochemistry test results or in urinalysis results between the 2 treatment groups. Eosinophilia related to atopy and neutrophilia and lymphocytosis, temporally related to intercurrent infections as recorded on the diary cards and case record forms, were the most common abnormal laboratory values identified. Overall, there was an age-appropriate decrease in transaminases during the 18 months of treatment in both the cetirizine- and placebo-treated children (Fig 4). A 14-month-old asymptomatic

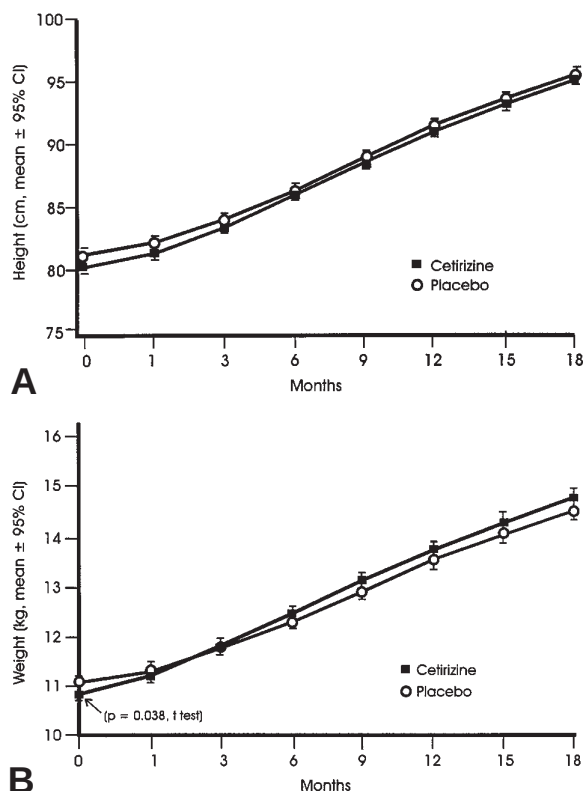


FIG 2. Height (A) and weight (B). Children in the cetirizine-treated group and in the placebo-treated group had age-appropriate gains in height and weight during the 18-month study. The cetirizine-treated children weighed significantly less than the placebo-treated children at the start of the study (t test, $P = .038$). At all other times of measurements, the differences in height and weight between the groups were not statistically significant. With repeated measures analysis of covariance, however, with age at baseline as the covariate, there was a statistically significant ($P < .001$) time effect, age effect, treatment-time interaction, and time-age interaction between the baseline visit and the last visit in the study for weight. At the final evaluation, the mean difference in weight between the cetirizine- and placebo-treated children was 250 g.

boy who was included in the study for 5 weeks, despite elevated transaminases at baseline, has been reported previously.⁶

DISCUSSION

H₁-antagonists, widely advertised directly to the public and available in liquid formulations without prescription, are generally considered to be safe for use in very young children. Contrary to this perception, old first-generation H₁-antagonists may cause a wide variety of adverse effects even when administered in recommended doses.^{1,11-19} They cross the blood-brain barrier and interfere with the neurotransmitter effect of histamine, potentially causing central nervous system symptoms such as somnolence, irritability, hyperactivity, hallucinations, insomnia or dystonia, and exacerbation of seizures.¹⁶ They also potentially cause anticholinergic effects, in-

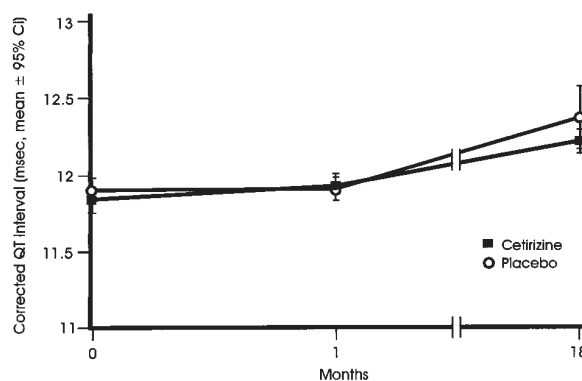


FIG 3. QTc interval (Bazett's correction for heart rate). Electrocardiograms were obtained at baseline and after 1 and 18 months of treatment or at the last visit if the child left the study early. With the use of repeated measures analysis of covariance, and age at baseline as the covariate, there was no statistically significant treatment effect, age effect, treatment-time interaction, or time-age interaction with regard to the QTc interval. The time effect on the QTc interval was significant; there was a significant change ($P = .003$) between baseline and final electrocardiograms in both the cetirizine- and placebo-treated groups, suggesting that Bazett's correction for heart rate is not entirely adequate in very young children.

cluding dry mouth and mucous membranes, urinary retention, decreased gastrointestinal motility, and gastrointestinal upset. Some, such as cyproheptadine and ketotifen, potentially cause antiserotonin effects and increase the appetite.^{1,17}

A few first-generation H₁-antagonists have been implicated as a cause of sudden infant death, although causality has never been proved.¹⁸ After overdose, first-generation H₁-antagonists may cause pupillary dilation, flushed face, fever, tachycardia, hypotension, seizures, coma, and death.^{1,11,15} Even when applied topically to the skin, first-generation H₁-antagonists such as diphenhydramine or promethazine can produce systemic toxicity and also place children at risk for sensitization and contact dermatitis to the antihistamine.¹⁹

Although the new second-generation H₁-antagonists are safer than their predecessors with regard to central nervous system toxicity, rarely, terfenadine and astemizole have been reported to cause cardiac toxicity in children, including ventricular arrhythmias and torsades de pointes.²⁰⁻²²

In this large, prospective, randomized, double-blind, placebo-controlled study in young children, a reassuring margin of safety has been documented for a new second-generation H₁-antagonist, cetirizine, during 18 months of regular treatment. Drop-outs as the result of symptoms or events and serious events, including hospitalizations, occurred infrequently. Most symptoms and events reported were due to intercurrent respiratory or gastrointestinal infections, exacerbations of allergic disorders, or age-related concern rather than to adverse effects. Sleep problems were infrequent, and there were no statistically significant differences between the cetirizine- and placebo-

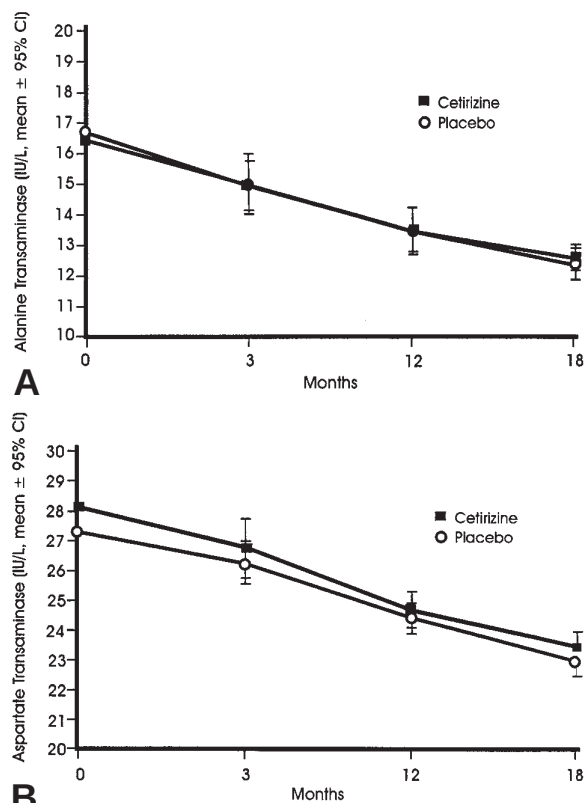


FIG 4. Alanine transaminase (**A**) and aspartate transaminase (**B**). During 18 months of treatment both alanine transaminase and aspartate transaminase declined in an age-appropriate manner (-2.9 IU/L and -3.8 IU/L in the cetirizine-treated children and -4.0 IU/L and -4.4 IU/L in the placebo-treated children; visit 1 to 8). There were no significant differences between the cetirizine- and placebo-treated children at any time ($P = .816$ for alanine transaminase and $P = .595$ for aspartate transaminase, Mann-Whitney U test) or for comparison of the 2 groups on the basis of the difference between baseline and the last available measurement.

treated children for insomnia or somnolence; an increased prevalence of sleep disturbances, including difficulty falling asleep, night waking because of itching and scratching, and daytime tiredness has been described previously in children with atopic dermatitis.²³ Also, there were no clinically relevant differences between the groups with regard to growth, developmental assessments, electrocardiograms, or laboratory tests. The cetirizine-treated children did, however, experience fewer admissions for asthma, fewer episodes of urticaria, fewer allergic reactions and decreased use of additional oral H_1 -antagonists.

The individualized doses of cetirizine administered in this study ranged from 4 mg in a child weighing 7.5 kg to 11 mg in a child weighing 24.5 kg and, on a milligram per kilogram basis, were therefore relatively high compared with those used in older children and adults. The rationale for these high doses and for twice daily administration of cetirizine to young children has been previously documented in clinical pharmacology studies.²⁴⁻²⁷ In infants with a mean age of 12.3 ± 5.4 months, the

mean cetirizine plasma elimination half-life is only 3 hours,²⁴ in contrast to mean elimination half-life values of 5 to 7 hours in children.^{25,27} The pharmacokinetics are characterized by rapid absorption, with peak plasma levels reached in 2 ± 1.3 hours in infants,²⁴ and less extensive biotransformation in the cytochrome P_{450} system than many other H_1 -antagonists, making the possibility of medication interactions unlikely. Therapeutic concentrations of cetirizine in the skin are attained promptly despite a low volume of distribution for cetirizine.^{28,29} In infants, a single cetirizine dose significantly suppresses histamine-induced skin wheal-and-flare responses for 12 hours²⁴; in contrast, in 8-year-old children, one dose suppresses the wheal-and-flare response completely for at least 24 hours.²⁷

Previous prospective clinical studies of cetirizine, like those performed with other H_1 -antagonists, have been of relatively short duration. In infants, the effect of cetirizine on sleep and sleep apnea has been assessed with polysomnographic recordings; compared with placebo, it did not significantly increase total sleep time or number and duration of obstructive events.³⁰ In allergic rhinitis or atopic dermatitis studies of 2 to 4 weeks duration in children aged 2 to 14 years, no significant differences in number or severity of adverse effects were found between the cetirizine- and placebo-treated groups,³¹⁻³⁶ and there was no evidence of dose-related adverse effects.^{31,34,35} In a double-blind, 4-week study in which 12-lead electrocardiograms were performed at intervals in 129 children aged 6 to 11 years, (44 children receiving cetirizine therapy 10 mg, 35 children receiving cetirizine therapy 5 mg, and 50 children receiving placebo therapy), the changes in the QTc interval were not significantly different among the 3 treatment regimens.³⁷

The ETAC Study is characterized by a low drop-out rate over 18 months, a relatively complete set of clinical assessments, electrocardiograms and laboratory data, good compliance with study medication, and few adverse effects despite high-dose cetirizine treatment. It is the first prospective, randomized, double-blind, placebo-controlled, long-term study of the safety of any H_1 -receptor antagonist in very young children. It is also the longest prospective, randomized, double-blind, placebo-controlled investigation of the safety of any H_1 -antagonist ever conducted in any age group. Allergic disorders are characterized by recurrent or persistent symptoms that may last for years, or for a lifetime, and long-term studies of the safety of pharmacologic treatment of these disorders are of considerable importance.

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