

Safety of cetirizine in infants 6 to 11 months of age: A randomized, double-blind, placebo-controlled study

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Background: H₁-antihistamines are widely used for symptom relief in allergic disorders in infants and children; however, there are few prospective, randomized, double-blind, controlled studies of these medications in young children, and to date, no such studies have been conducted in infants.

Objective: This prospective, randomized, parallel-group, double-blind, placebo-controlled study was designed to evaluate the safety of the H₁-antihistamine cetirizine, particularly with regard to central nervous system and cardiac effects, in infants age 6 to 11 months, inclusive.

Methods: Infants who met the entry criteria for age and had a history of treatment with an H₁-antihistamine for an allergic or other disorder were randomized to receive 0.25 mg/kg cetirizine orally or matching placebo twice daily orally for 1 week.

Results: The mean daily dose in cetirizine-treated infants was 4.5 ± 0.7 mg (SD). No differences in all-cause or treatment-related adverse events were observed between the cetirizine- and placebo-treated groups. A trend was observed toward fewer adverse events and sleep-related disturbances in the cetirizine group compared with the placebo group. No prolongation in the linear corrected QT interval was observed in cetirizine-treated infants compared with either baseline values or with values in placebo-treated infants.

Conclusions: We have documented the safety of cetirizine in this short-term investigation, the first randomized, double-blind, placebo-controlled study of any H₁-antihistamine in infants. Additional prospective, randomized, double-blind, placebo-controlled, long-term studies of cetirizine and other H₁-antihistamines are needed in this population. (*J Allergy Clin Immunol* 2003;111:1244-8.)

Key words: H₁-antihistamine, cetirizine, somnolence, electrocardiogram, infant, early treatment of the atopic child

H₁-antihistamines, introduced for clinical use more than 60 years ago, are widely administered for symptom relief in allergic rhinitis, urticaria, and atopic dermatitis in patients of all ages, including infants, although the

Abbreviation used
 ECG: Electrocardiogram

precise rate of occurrence of these disorders in infants has not been established.¹ There are no randomized, double-blind, placebo-controlled studies of H₁-antihistamines in patients younger than 1 year of age.¹ Despite the lack of an evidence base for H₁-antihistamine use in infants, most parents and care givers and, indeed, many health care professionals assume that these medications have been adequately tested and are safe for use in this population. This is in large part because of their ubiquitous availability in liquid formulations, including infant drops, and their widely advertised, nonprescription, over-the-counter availability.

In comparison with other H₁-antihistamines, the safety²⁻⁶ and efficacy^{2,7-9} of cetirizine, a piperazine H₁-antihistamine used for the treatment of allergic rhinitis and urticaria, has been relatively well studied in young children. In the prospective, randomized, double-blind, placebo-controlled, parallel-group Early Treatment of the Atopic Child study conducted over 18 months in 817 children with atopic dermatitis age 12 to 24 months at study entry, cetirizine was found to have a similar safety profile to that of placebo and did not affect behavioral, cognitive, or psychomotor development.³⁻⁵ It was also found to have a significant topical glucocorticoid-sparing effect in atopic dermatitis,⁷ to reduce acute urticaria episodes significantly,⁸ and to delay asthma onset in children who were sensitized to grass pollen or to house dust mites at study entry.⁹ Small, open-label, single-dose studies of cetirizine have been performed in patients as young as age 6 months; however, because these studies were not randomized, double-blind, or placebo-controlled,^{10,11} additional investigation of the safety of cetirizine is needed in infants.

We hypothesized that cetirizine and placebo would have similar safety profiles in infants. We tested this hypothesis in a prospective, multicenter, randomized, parallel-group, double-blind, placebo-controlled study.

METHODS

The purpose of this research was to evaluate cetirizine safety in infants age 6 to 11 months, inclusive, with particular emphasis on central nervous system and cardiac safety. The study was conducted

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in accordance with the 1996 revision of the Declaration of Helsinki, and the International Conference on Harmonization/Good Clinical Practices Guidelines were followed. Approval was obtained from the institutional review boards and independent ethics committees of all 16 academic medical centers and private pediatric practices involved. Written informed consent of parents or legal guardians was obtained for the participation of their infants in this study.

For inclusion in the study, the infants were required to be outpatients who had a history of H₁-antihistamine treatment for allergic rhinitis, urticaria, atopic dermatitis, or other disorders.

Exclusion criteria included body weight or length below the fifth percentile; history of sleep apnea or a sibling with sleep apnea or sudden infant death syndrome; and allergy or intolerance to cetirizine, any of its constituents, or other piperazine H₁-antihistamines. Infants were also excluded if they needed to use one or more of the following medications within the time period specified before enrollment: H₁-antihistamines or cough/cold preparations within 7 days, systemic corticosteroids within 28 days, and systemic antibiotics within 7 days. In addition, infants were excluded if they had a QTc interval of greater than 450 ms or if their parents/caregivers were unlikely to record observations reliably or had evidence of alcohol or drug dependence.

Before randomization, the infant's complete medical history was obtained from the parent/caregiver, and baseline symptoms relating to sleep patterns, irritability, and tremor were recorded. A physical examination was performed, and vital signs (heart rate, blood pressure, respiration rate, and temperature) were recorded. The baseline QT interval was measured on a 12-lead electrocardiogram (ECG) and corrected for heart rate by using the Fridericia formula.²

Study medication was orally administered twice daily for 7 days at 12-hour intervals (morning and evening) with a calibrated syringe. The first dose of either 0.25 mg/kg cetirizine or matching placebo was administered in the clinic. In the diary provided, administration of daily doses was recorded and parents/caregivers answered yes or no to questions about changes in sleep pattern, nervousness, irritability, or tremor during the previous 24 hours.

At the second and last visit, conducted 7 days after the initial visit or at early withdrawal, another complete physical examination, including vital signs, was performed, and a 12-lead ECG was obtained approximately 2 hours after the last dose of the study drug. Adherence was determined by measuring the volume of unused study medication, review of the daily diary, and interview of the parent/caregiver. Review of information in the diary and interview were also used to determine the incidence of adverse events. A follow-up telephone interview was conducted 7 days after the second visit to assess subsequent adverse events.

In the ECGs obtained at baseline and at visit 2, digital measurements were used to derive and record the data. All ECGs were transmitted electronically to SpaceLabs Medical Data (Redmond, Wash) and evaluated by a pediatric cardiologist who was blinded to the infant's treatment group assignment.

All treatment-emergent adverse events were recorded and analyzed by age group (6-8 months and 9-11 months, both inclusive), irrespective of whether they were related to study medication. Causality and severity were assessed and recorded by the investigator, and all events were followed until resolution. The mean daily dose administered and adverse events were also analyzed by age group.

Since this was the first randomized, double-blind, placebo-controlled study of any H₁-antihistamine in infants age 6 to 11 months, it was not possible to perform sample size calculations. The sample size was therefore determined empirically, and with 85 infants enrolled in a study that includes an objectively measured outcome (ECG monitoring), it is comparable with the number of adults enrolled in Phase I or Phase II clinical trials.

TABLE I. Description of infants at study entry

	Cetirizine, mean (range)	Placebo, mean (range)
Demographics (mean and range)		
Boys (n)	21	20
Age (mo)	8.5 (6.0-11.0)	8.0 (6.0-11.0)
Weight (kg)	9.3 (7.2-12.5)	9.3 (7.5-12.6)
Length (cm)	73.2 (66.9-81.0)	71.3 (65.0-78.0)
Girls (n)	21	23
Age (mo)	7.9 (6.0-11.0)	7.2 (5.0-10.0)*
Weight (kg)	8.6 (6.9-10.6)	8.2 (6.8-10.7)
Length (cm)	69.7 (65.0-76.0)	68.7 (65.0-75.0)
Entry criteria		
Total no. of infants (n)	42	43
Diagnosis of allergic disorder/antihistamine use (n)	31	34
Allergic rhinitis (n)	20	18
Atopic dermatitis (n)	5	10
Urticaria (n)	0	0
Other† (n)	6	6
Prior antihistamine use for other disorder (n)	11	9

*One infant was 1 day short of being 6 months old at the time of study entry.

†For example, contact dermatitis.

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Daily diaries were analyzed descriptively according to treatment group on the basis of the overall number of responses available for each question and the percentage of parents/caregivers who responded yes to each question. The mean changes from baseline in the QT interval, corrected for heart rate by using a linear regression formula,¹² were compared between treatment groups by using a 2-sample, 2-sided *t* test with a 5% significance level.

RESULTS

Ninety infants were screened, and 85 were randomized to treatment with cetirizine or placebo. The distribution of the infants between the 2 treatment groups was similar with respect to demographics and clinical diagnoses (Table I). Twenty-seven (64.3%) of the 42 infants in the cetirizine group and 29 (67.4%) of the 43 infants in the placebo group had been treated with at least one H₁-antihistamine for an allergic disorder before study entry; the remaining infants (11 in the cetirizine group and 9 in the placebo group) had received an H₁-antihistamine for a nonallergic disorder.

Seventy-six (89.4%) infants completed the study. Nine infants (5 in the cetirizine group and 4 in the placebo group) were withdrawn: 3 (1 in the cetirizine group and 2 in the placebo group) for study medication-related adverse events, 3 (2 in the cetirizine group and 1 in the placebo group) for adverse events not related to medication, and 3 (2 in the cetirizine group and 1 in the placebo group) for administrative reasons (ie, withdrawn consent, protocol violation, or study medication bottle broken). All infants who were given one or more doses of study medication were included in the safety analysis. The mean total daily dose was calculated on the basis of the volume of unused study medication for infants age 6 to

TABLE II. Adverse events*

	All-cause adverse events		Treatment-related adverse events	
	Cetirizine	Placebo	Cetirizine	Placebo
No. (%) of infants with adverse events	31/42 (73.8)	38/43 (88.4)	19/42 (45.2)	27/43 (62.8)
No. of adverse events	63	85	38	59

*Some infants might have had more than 1 event.

TABLE III. Incidence of adverse events* occurring in 2 or more infants in each treatment group

	All-cause adverse events		Treatment-related adverse events	
	Cetirizine, n (% of 42)	Placebo, n (% of 43)	Cetirizine, n (% of 42)	Placebo, n (% of 43)
Nervousness	12 (28.6)	19 (44.2)	12 (28.6)	18 (41.9)
Insomnia	10 (23.8)	19 (44.2)	9 (21.4)	17 (39.5)
Somnolence	9 (21.4)	13 (30.2)	8 (19.1)	12 (27.9)
Toothache†	4 (9.5)	4 (9.3)	0	0
Diarrhea	3 (7.1)	4 (9.3)	3 (7.1)	3 (7.0)
Otitis media	3 (7.1)	2 (4.7)	0	0
URTI	3 (7.1)	1 (2.3)	0	0
Agitation	2 (4.8)	7 (16.3)	2 (4.8)	5 (11.6)
Tremor	2 (4.8)	2 (4.7)	1 (2.4)	1 (2.3)
Fever	2 (4.8)	2 (4.7)	0	0
Cough	0	2 (4.7)	0	0
Pharyngitis	2 (4.8)	0	0	0
Rash	1 (2.4)	2 (4.7)	0	0
Rhinitis	2 (4.8)	2 (4.7)	1 (2.4)	0

URTI, Upper respiratory tract infection.

*Some infants might have had more than 1 event.

†Teething-associated.

TABLE IV. Summary of overall responses in daily diary entries by infants' parents or guardians

Change from baseline: no. responding yes	Cetirizine, n (% of 41)	Placebo, n (% of 43)
Abnormal increase in sleep	12 (29.3)	13 (30.2)
Abnormal decrease in sleep	10 (24.4)	16 (37.2)
Abnormal restlessness during sleep	16 (39.0)	22 (51.2)
Abnormal irritability/fussiness	19 (46.3)	20 (46.5)
Tremor	2 (4.9)	2 (4.7)

11 months, as well as for those age 6 to 8 months and 9 to 11 months. In the cetirizine-treated group, the mean daily dose administered to infants age 6 to 11 months, inclusive, was 4.5 ± 0.7 mg (range, 3.4-6.2 mg); in those age 6 to 8 months, it was 4.1 ± 0.5 mg, and in those age 9 to 11 months, it was 5.0 ± 0.6 mg. In the placebo-treated group the mean daily dose equivalents were 4.4 ± 0.6 mg (range, 3.4-6.4 mg) in infants age 6 to 11 months, 4.2 ± 0.4 mg in those age 6 to 8 months, and 4.9 ± 0.7 mg in those age 9 to 11 months.

A total of 63 adverse events were reported in 31 infants in the cetirizine group compared with 85 adverse events reported in 38 infants in the placebo group (Table II).

Adverse events were considered to be mild to moderate in all cases except for one severe event in a placebo-treated infant who had an increase in cough that resolved 7 days after withdrawal from the study and was not considered to be related to study medication.

Table III shows the incidence of adverse events occurring in 2 or more cetirizine- or placebo-treated infants:

nervousness, insomnia, and somnolence were the most frequently reported all-cause and treatment-related events in both treatment groups. The age-group analysis of the most common adverse events paralleled that of the treatment-emergent events. All-cause and treatment-related adverse events were generally more frequent in the 6- to 8-month age group than in the 9- to 11-month age group, with nervousness, insomnia, and somnolence the most frequently reported events in both age groups. The summary of daily diary entries by infants' parents or guardians did not reveal any differences between the groups for increase in sleep, decrease in sleep, restlessness during sleep, abnormal irritability or fussiness, or tremor (Table IV).

Median changes in values from baseline for vital signs are shown in Table V. Mean PR, QRS, and QT intervals, measured at baseline and at endpoint, are shown in Table VI. Minor changes from baseline occurred in these ECG parameters in some infants; however, no clinically relevant changes were observed in any infant. The mean

TABLE V. Median changes from baseline to endpoint for vital signs

	Cetirizine		Placebo	
	Baseline	Median change	Baseline	Median change
Heart rate, beats/min (n)	126 (41)	4	130 (43)	0
Systolic blood pressure, mm Hg (n)	82 (38)	1	86 (43)	0
Diastolic blood pressure, mm Hg (n)	52 (38)	2	52 (42)	1
Respiration, breaths/min (n)	26 (41)	0	28 (42)	0
Temperature, °C (n)	36 (41)	0	36 (43)	0

Blood pressure and heart rate measurements were performed with the infants in the supine position.

TABLE VI. Mean $\pm$ SD ECG parameters at baseline and endpoint

	Cetirizine (n = 40)		Placebo (n = 42)	
	Baseline	Endpoint	Baseline	Endpoint
PR interval (ms)	118.9 $\pm$ 17.2	114.9 $\pm$ 14.7	109.9 $\pm$ 13.9	114.2 $\pm$ 18.8
QRS interval (ms)	67.0 $\pm$ 9.0	65.2 $\pm$ 8.3	65.4 $\pm$ 9.4	71.0 $\pm$ 29.1
QT interval (ms)	261.5 $\pm$ 21.7	257.4 $\pm$ 15.6	254.3 $\pm$ 18.2	258.2 $\pm$ 17.4
QT _{LC} (ms)	414.3 $\pm$ 12.3	414.2 $\pm$ 13.5	415.7 $\pm$ 10.8	416.4 $\pm$ 10.4

QT_{LC}, Linear corrected QT interval.

change from baseline in the linear corrected QT interval was 0.7 ms in both treatment groups. By using a 2-sample *t* test to compare the mean change in linear corrected QT interval from baseline to endpoint between the 2 treatment groups, no significant prolongation by cetirizine ($P = .98$; 95% CI for mean difference between the groups, -4.74 to 4.60) was found.

DISCUSSION

Here we document the safety of 0.25 mg/kg cetirizine twice daily in a very young pediatric population, specifically in infants age 6 to 11 months, inclusive, by using a prospective, randomized, parallel-group, double-blind, placebo-controlled study design. The relatively high dose of cetirizine administered (0.25 mg/kg twice daily, mean total daily dose of 4.5 ± 0.7 mg) was based on a single-dose pharmacokinetic-pharmacodynamic study of cetirizine in infants and children age 6 to 23.5 months,¹⁰ in whom a shorter elimination half-life of 3.1 ± 1.8 hours and a more rapid total body clearance (apparent) of 2.13 ± 1.15 mL/min/kg were found compared with values in older children.² The information obtained in this pharmacokinetic-pharmacodynamic study¹⁰ also provided the rationale for administering 0.25 mg/kg cetirizine twice daily in the Early Treatment of the Atopic Child study.^{3-5,7-9}

The cetirizine- and placebo-treated groups were similar with regard to the number of infants with adverse events, the number of adverse events regardless of causality, and the number of treatment-related adverse events. Many of the infants' symptoms were related to intercurrent infections reported as upper respiratory tract infections, otitis media, diarrhea, fever, cough, and pharyngitis or to age-related events, such as toothache caused by teething. In both cetirizine- and placebo-treated infants, the incidence of all events was higher in those age 6 to 8 months than in those age 9 to 11 months.

Where differences were observed between the treatment groups, the results consistently favored cetirizine safety (eg, for number of infants with adverse events, total number of adverse events, and number of infants with abnormal decrease in sleep and increase in restlessness). In both treatment groups the most commonly reported adverse events were related to the central nervous system and included nervousness, insomnia, and somnolence. In both of the groups, most of these events were considered by the investigators to be related to treatment. Reduction in sleep disturbances in the active treatment group might have been due to the effect of cetirizine on reducing itching and scratching in infants with atopic dermatitis and reducing nasal symptoms in infants with allergic rhinitis. There is also the possibility that reduced sleep disruption might have been due to sedation from cetirizine; however, in young children cetirizine is not significantly more sedating than placebo,^{2,3} and in infants if an H₁-antihistamine affects the central nervous system, it often causes paradoxical stimulation rather than sedation.^{13,14}

The small changes in vital signs observed in the infants in each group were not considered to be clinically relevant because normal blood pressure and respiration rates can vary widely and might be dependent on whether the infant is awake or asleep. Cetirizine-treated infants had no statistically or clinically significant changes in ECG values (heart rate, PR interval, QRS interval, or QT interval) compared with pretreatment baseline values or with values in placebo-treated infants.

H₁-antihistamines are among the most commonly used medications for relief of itching and other symptoms in infants and children with allergic rhinitis, atopic dermatitis, urticaria, and other disorders, which have a high morbidity in the pediatric population, contributing to sleep loss, irritability, inattention, and learning deficits.¹⁵⁻²⁰ First-generation H₁-antihistamines are available in a variety of palatable liquid formulations for use in infants and young children. In

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this vulnerable population, although these medications are assumed to be safe and effective, their safety has never been documented in prospective, randomized, double-blind, placebo-controlled trials because most of them were introduced in the 1940s and 1950s, before such trials were required by regulatory agencies. The true incidence of adverse effects after manufacturers' recommended doses of first-generation H₁-antihistamines in infants and children is unknown. Toxicity and fatality after overdose have been documented in case reports and toxicology registries.^{1,13,14,21-29} These old H₁-antihistamines cross the blood-brain barrier and have varying proclivities to cause fatigue, lassitude, somnolence, lethargy, and impairment of cognitive functioning. In infants and young children they might also have paradoxical stimulatory effects on the central nervous system and cause irritability, nervousness, hyperactivity, and seizures by interfering with the natural anticonvulsant effect of histamine.^{13,14} Some of them, such as promethazine, have been associated with apnea and sudden death in infants, although no cause-and-effect relationship has been established.²⁵⁻²⁷

In contrast, in randomized, double-blind, placebo-controlled trials the safety of several of the new second-generation H₁-antihistamines, including cetirizine^{1,2,30-32} and loratadine,^{1,33} has been documented in children as young as age 24 months, and the safety of cetirizine^{3-6,11} has been documented in even younger children. The present short-term investigation, which is the first prospective, randomized, double-blind, placebo-controlled safety study of any H₁-antihistamine in infants, is an important step forward in assessing the safety of H₁-antihistamines in this population and serves as the basis for Food and Drug Administration approval of cetirizine for use in patients as young as age 6 months. Additional prospective, randomized, double-blind, placebo-controlled studies of cetirizine and other H₁-antihistamines are needed in infants.

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