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Safety of levocetirizine treatment in young atopic children: An 18-month study

Simons FER on Behalf of the Early Prevention of Asthma in Atopic Children (EPAAC) Study Group. Safety of levocetirizine treatment in young atopic children: An 18-month study.
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There are more than 40 H_1-antihistamines available worldwide. Most of these medications have never been optimally studied in prospective, randomized, double-masked, placebo-controlled trials in children. The aim was to perform a long-term study of levocetirizine safety in young atopic children. In the randomized, double-masked Early Prevention of Asthma in Atopic Children Study, 510 atopic children who were age 12–24 months at entry received either levocetirizine 0.125 mg/kg or placebo twice daily for 18 months. Safety was assessed by: reporting of adverse events, numbers of children discontinuing the study because of adverse events, height and body mass measurements, assessment of developmental milestones, and hematology and biochemistry tests. The population evaluated for safety consisted of 255 children given levocetirizine and 255 children given placebo. The treatment groups were similar demographically, and with regard to number of children with: one or more adverse events (levocetirizine, 96.9%; placebo, 95.7%); serious adverse events (levocetirizine, 12.2%; placebo, 14.5%); medication-attributed adverse events (levocetirizine, 5.1%; placebo, 6.3%); and adverse events that led to permanent discontinuation of study medication (levocetirizine, 2.0%; placebo, 1.2%). The most frequent adverse events related to: upper respiratory tract infections, transient gastroenteritis symptoms, or exacerbations of allergic diseases. There were no significant differences between the treatment groups in height, mass, attainment of developmental milestones, and hematology and biochemistry tests. The long-term safety of levocetirizine has been confirmed in young atopic children.

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Many medications that are assumed to be safe and effective in children have, in fact, never actually been studied adequately in prospective, randomized, double-masked, placebo-controlled clinical trials in children (1). Such studies are critically important, because developmental changes may profoundly affect the absorption, metabolism, elimination, and action of medications (2).

There are more than 40 H_1-antihistamines in use around the world. They potentially cause adverse effects not only through H_1-receptors in the central nervous system and elsewhere, but also through muscarinic, alpha-adrenergic, and serotonin receptors, and through cardiac ion channels (3, 4). Although they are widely used, sometimes for months or years on end, and are assumed to be safe, surprisingly little data have been published regarding their long-term safety in patients of any age, including children (5, 6).

We hypothesized that the piperazine H_1-antihistamine levocetirizine would have a similar safety profile to that of placebo in young atopic children. We tested this hypothesis in an 18 month-long randomized, double-masked, placebo-controlled parallel-group study. Other out-

comes of this study, including the lack of efficacy of levocetirizine treatment on preventing or delaying asthma (the primary endpoint), and the efficacy of levocetirizine in preventing urticaria (a secondary endpoint), as well as epidemiologic investigations in the study population, will be published separately.

Methods

The Early Prevention of Asthma in Atopic Children (EPAAC) Study protocol was approved by the Institutional Review Board in each of the participating centers in 10 European countries, Australia, and South Africa. The children were enrolled after informed consent was obtained from their parent(s) or guardian(s).

The study had a randomized, double-masked, parallel-group, placebo-controlled, multi-center design. Children were included if they were age 12–24 months, had atopic dermatitis, elevated specific IgE to either grass pollen or house dust mite, and a family history of allergy. Assignment to treatment was made according to pre-selected randomization factors at baseline, including: status of sensitization to grass pollen or house dust mite, sensitization to egg, maternal history of asthma, and country of residence.

Children were excluded if they had asthma or any other systemic disease; if their height or body mass were below the 5th percentile; if they had any severe neurologic or psychologic disorder requiring medical treatment; if they were known to be intolerant of levocetirizine or any other piperazine antihistamine, or to the parabens used as preservatives in H_1-antihistamine liquid formulations; if they had a personal history or sibling history of sleep apnea; or if they had renal insufficiency or any metabolic condition that might affect the elimination of levocetirizine. Regular treatment with other H_1-antihistamines was discontinued before study entry.

During an 18-month period, 255 children received treatment with levocetirizine drops 0.125 mg/kg b.i.d., and 255 children received matching placebo drops twice daily. On diary cards, parents or guardians recorded the adverse events, as well as the days on which symptoms of asthma or urticaria were observed, and the days on which medication was given. This information was validated and entered into the electronic case report form by the study coordinator during regular telephone monitoring, eight scheduled visits, and additional medical visits as needed during the 18-month treatment period. Treatment–emergent adverse events were described by the investigators according to primary system organ class, using preferred terminology, coded with the Medical Dictionary for Regulatory Activities (MEDRA).

Throughout the study, without knowledge of treatment group assignment, an independent Scientific Advisory Board performed safety monitoring at regularly scheduled meetings twice yearly, and by e-mail correspondence between meetings. Data reviewed included: standardized reports of serious adverse events, frequent adverse events, events judged by the investigator as being possibly related to study medication, and events leading to permanent discontinuation.

A *serious adverse event* was defined as any untoward medical occurrence that at any time was life-threatening, or resulted in hospitalization, persistent or significant disability, or death. In addition, any important medical event that might jeopardize the child or require intervention to prevent one of the outcomes listed above was reported as a serious adverse event. An *adverse event* was captured by spontaneous reporting on the diary cards, and also by asking the child's caregiver, at each scheduled visit, 'Did you notice anything unusual about the child's health since the last visit?' and recording their response. An *overdose* was defined as a single intake of study medication of 0.5 mg/kg or more.

At each visit, all medication bottles previously dispensed were returned whether empty, partly-used, or not used, and drug reconciliation was performed in the presence of the child's caregiver. Study medication intake was then assessed by measuring the weight of each bottle returned and subtracting the weight from that of the bottle at the time of dispensing.

Psychomotor development was assessed by asking the caregiver about the child's developmental milestones, using a questionnaire administered at the regularly scheduled visits. Questions about gross motor development included the age at which the child: sat alone, crawled, stood alone, walked alone, climbed stairs with assistance, climbed stairs alone, and ran. Questions about fine motor development included the age at which the child first showed evidence of pincer (two finger) grip, pencil (three finger) grip, ability to match cubes (build a four-block tower), and right/left hand preference. Questions about speech and language development included the age at which the child first pronounced five separate words, named many objects, and spoke in short sentences. In a subset of children from the UK and Australia, the McArthur Communicative Development Inventory (MCDI) test, the Parent Report of Children's Abilities (PARCA) test, and the Behavior Checklist test

were also administered, and will be reported separately.

At baseline, and after 18 months of levocetirizine or placebo treatment, EMLA cream was applied to a selected skin site, and a blood sample (8 and 10 ml, respectively) was obtained by direct venipuncture. Laboratory tests monitored for safety included: hemoglobin, hematocrit, platelet count, white blood cell, and differential; aspartate transaminase (serum glutamic-oxaloacetic transaminase), alanine transaminase (serum glutamate pyruvate transaminase), total bilirubin, total protein, creatinine, and C-reactive protein.

If the child discontinued the study early, all tests scheduled for the 18-month visit were performed at the time of discontinuation, that is, at the last study visit.

Statistical analysis

Safety variables were listed individually for detailed clinical review. Laboratory values, height and mass, and changes from baseline in laboratory values and in height and mass were presented descriptively by treatment group, with 95% CI calculated on the median.

Adverse events were summarized descriptively by treatment group, organ class, and preferred term, and also were summarized by severity, relationship to study medication, and withdrawal from the study. Developmental milestones were analyzed descriptively by treatment group. All safety analyses were performed on the intention-to-treat population, defined as all randomized children who received at least one dose of study medication.

Results

There were 510 children in the intention-to-treat population: 255 (mean age 19.3 ± s.e.m. 0.3 months, 60.8% boys) in the levocetirizine treatment group, and 255 (mean age 19.4 ± s.e.m. 0.2 months, 64.3% boys) in the placebo treatment group. Two hundred nineteen (85.9%) of the children who received levocetirizine and 216 (84.3%) of the children who received placebo completed 18 months of treatment. In the levocetirizine-treated children, the total daily dose ranged from 2.825 mg to 3.830 mg. Assessment of adherence, as reflected in accurate assessment of study medication intake, was possible for about 60% of the children and was calculated to be: 97.8% ± s.d. 27.6% in those treated with levocetirizine, and 97.0% ± s.d. 17.9% in those treated with placebo.

Overall, adverse events occurred with similar frequency in both treatment groups, as summarized in Table 1. There were no deaths, and no overdoses of study medications.

As detailed in the diary cards and electronic case report forms, adverse events occurred in most of the children in the study during 18 months active treatment. These events were generally mild, and occurred with similar frequency in the two treatment groups (Fig. 1). The events reported most frequently were: upper respiratory tract infections (URTI) and similar or related events that were described verbatim by the investigators as nasopharyngitis, rhinitis, pharyngitis, otitis media, ear infection, tonsillitis, viral infection, rhinorrhea, laryngitis, viral URTI, and acute tonsillitis. Pyrexia (fever), gastroenteritis, vomiting and diarrhea were also common. In addition, cough, bronchitis, allergic rhinitis, conjunctivitis, worsening atopic dermatitis, and seasonal allergies were frequently reported, as were varicella and teething. Adverse events relating to the central nervous system were infrequent (Table 2). Febrile convulsions were more commonly reported in the levocetirizine-treated children, and behavioral problems and irritability were more frequently reported in the placebo-treated children.

Serious adverse events occurred in 12.2% of levocetirizine-treated children and 14.5% of placebo-treated children (Table 3). A 30-month-old girl developed lymphadenopathy and was diagnosed with acute lymphoblastic leukemia. The child was discontinued from the study. The

Table 1. Adverse events: summary

	Levocetirizine	Placebo
Intention-to-treat population	255 (100%)	255 (100%)
Deaths	0	0
Overdoses of study medication	0	0
One or more adverse events	247 (96.9%)	244 (95.7%)
Treatment-attributed adverse events	13 (5.1%)	16 (6.3%)
Serious adverse events	31 (12.2%)	37 (14.5%)
Treatment-attributed serious adverse events	0	1 (0.4%)*
Adverse events that led to discontinuation (treatment–emergent)	5 (2.0%)†	3 (1.2%)‡

*Hepatic enzyme increases were considered to be related to study medication.
†Levocetirizine-treated children permanently discontinued the study medication because of: allergic reaction, 'allergy aggravated'; weight increase, tonsillitis/dehydration, and acute lymphoblastic leukemia.
‡Placebo-treated children permanently discontinued the study drug because of worsening atopic dermatitis, increased hepatic enzymes, and varicella infection.

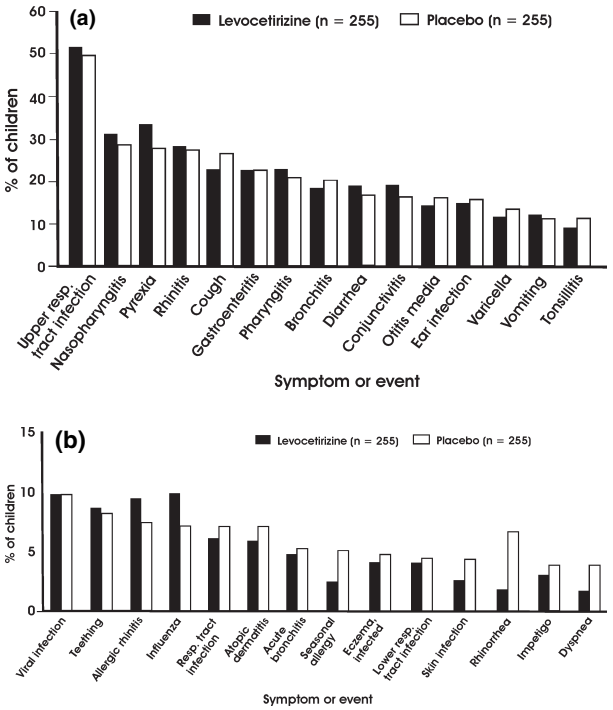

Fig. 1. Percent of children with treatment–emergent adverse events, as described by investigators (MEDRA preferred terms). (a) Adverse events having an incidence of at least 10% in one of the treatment groups. (b) Events having an incidence of at least 3.0% in one of the treatment groups. Note that the scales on the vertical axes differ in Fig. 1a,b.

Table 2. Neurologic/behavioral events

	Levocetirizine*	Placebo*
Abnormal behavior	2 (0.8%)	3 (1.2%)
Aggression	0	1 (0.4%)
Agitation	1 (0.4%)	0
Anxiety	0	1 (0.4%)
Burning sensation	0	1 (0.4%)
Convulsions	1 (0.4%)	0
Epilepsy	1 (0.4%)	0
Febrile convulsions	5 (2.0%)	1 (0.4%)
Headache	1 (0.4%)	4 (1.6%)
Insomnia	3 (1.2%)	2 (0.8%)
Irritability	0	4 (1.6%)
Nervousness	1 (0.4%)	0
Nightmare	0	1 (0.4%)
Sleep disorder	1 (0.4%)	1 (0.4%)
Somnolence	0	1 (0.4%)
Syncope	0	1 (0.4%)

*Two hundred fifty-five children in each treatment group.
Treatment–emergent adverse events, described by investigators by primary system organ class, using preferred terminology, coded with the Medical Dictionary for Regulatory Activities.

relationship to the study medication was judged as unlikely by the investigator and the Scientific Advisory Board. The study code was broken due to the serious nature of this disease, and the child was found to have been taking levocetirizine 1.75 mg/day. She responded to chemotherapy.

Table 3. Serious adverse events

Event	Levocetirizine	Placebo
Wheezing	12 (4.7%)	19 (7.5%)
Dermatitis, atopic	3 (1.2%)	6 (2.4%)
Gastroenteritis	2 (0.8%)	5 (2.0%)
Cough	4 (1.6%)	2 (0.8%)
Bronchopneumonia	4 (1.6%)	1 (0.4%)
Febrile convulsion	4 (1.6%)	0
Urticaria	1 (0.4%)	3 (1.2%)
Bronchitis, chronic	0	3 (1.2%)
Pneumonia	2 (0.8%)	0

In addition to the above serious adverse events, each of which occurred in more than one child in one of the treatment groups, other events each occurred in only one child (0.4%) of the 255 treated with levocetirizine, as reported verbatim by the investigators. These events included: acute tonsillitis, bronchitis, acute bronchitis, angioneurotic edema, concussion, convulsion, dehydration, dyspnea, food poisoning, head injury, lower respiratory tract infection, lymphoblastic leukemia (acute), patent ductus arteriosus, pyelonephritis, skin infection, tonsillitis, upper respiratory tract infection (URTI), viral URTI, vomiting, and weight increase.
Other serious adverse events, each occurring in only one child (0.4%) of the 255 treated with placebo, as reported verbatim by the investigators, included: angioneurotic edema, asthma, constipation, diarrhea, dyspepsia, dyspnea, eczema (infected), food allergy, gastroenteritis (rotavirus), *Haemophilus influenzae* infection, hepatic enzymes increase, hypersensitivity, pyelonephritis (acute), rectal polyp, subcutaneous abscess, and viral infection.

Four children presented with febrile convulsions described as serious adverse events. Their preceding febrile illnesses were: pyelonephritis, gastroenteritis, otitis media, or URTI. The relationship of the convulsions to the study medication was judged to be unlikely for all four children, and they all completed the study. When the medication code was broken at the end of the study, they were found to be in the levocetirizine treatment group. One of these children, whose brother had a history of epilepsy, subsequently developed recurrent convulsions and was also diagnosed with epilepsy.

Few adverse events were assessed by the investigators as being treatment-related (Table 1). Permanent discontinuation of study medications because of adverse effects was infrequent, occurring in 2.0% of levocetirizine-treated children and 1.2% of placebo-treated children (Table 1); more often, it was due to withdrawal of consent (8.6% and 8.2%, respectively), being lost to follow-up (1.6% and 3.1%, respectively), or other reasons including protocol violation (1.6% and 3.2%, respectively).

Age-appropriate physiologic increases in height and in body mass occurred over the 18 months of the study. There were no significant differences in height or in mass between the levocetirizine- and placebo-treated children at any time (Fig. 2).

Developmental milestones were reached at appropriate ages for gross motor skills, fine

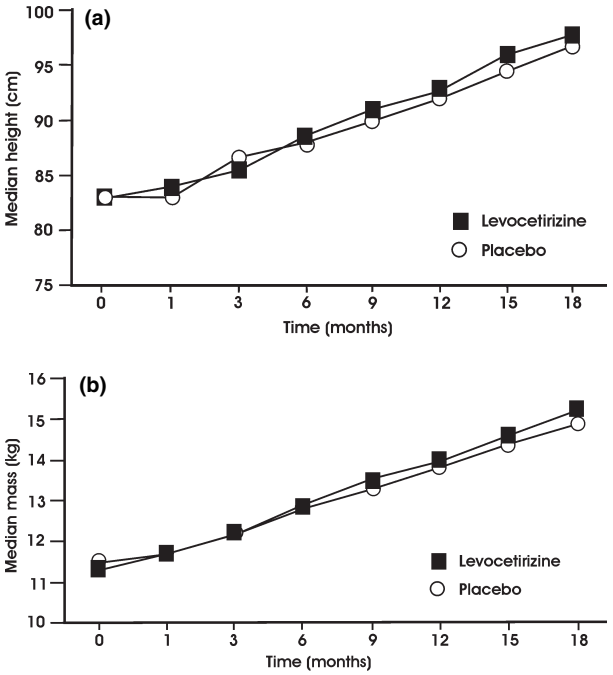

Fig. 2. Line graphs showing: (a) mean height in cm ± s.e.m. over 18 months of treatment with levocetirizine (n = 255) or placebo (n = 255). (b) Mean mass in kg ± s.e.m. over 18 months.

motor skills, and speech and language skills (Table 4). There were no significant differences between the levocetirizine-treated children and the placebo-treated children in the attainment of any milestone.

Nine hundred forty-one of an anticipated 1,020 blood samples were obtained and analyzed; 476 in levocetirizine-treated children and 465 in placebo-treated children. Age-appropriate physiologic changes in hematology and chemistry tests were documented over 18 months from baseline to the end of treatment. The median changes in the laboratory test results from baseline to the end of treatment are shown in Table 5. There were no significant differences between levocetirizine- and placebo-treated children.

Table 4. Developmental milestones

	Levocetirizine	Placebo
Median age in months (range) when child first performed this action		
Gross motor development		
Sit alone	6 (6–7)	6 (6–8)
Crawl	8 (7–10)	8 (7–10)
Stand alone	10 (9–12)	10 (9–12)
Walk alone	12 (11–14)	12 (11–14)
Climb stairs with assistance	14 (12–16)	14 (13–17)
Climb stairs without assistance	17 (14–20)	18 (15–20)
Run	16 (14–18)	16 (14–19)
Fine motor development		
Pincer (2-finger) grip	10 (8–13)	11 (7–14)
Pencil (3-finger) grip	17 (12–21)	18 (12–21)
Match cubes (build 4 block tower)	18 (14–20)	18 (14–20)
Show hand preference	17 (12–23)	18 (12–22)
Speech and language		
Pronounce first five words	14 (12–18)	15 (12–18)
Name many objects	18 (15–22)	18 (16–22)
Pronounce short sentences	22 (19–25)	23 (20–25)

Discussion

This study was characterized by a low drop-out rate over 18 months, adherence to study medication administration, few adverse effects attributed to study medication or leading to permanent discontinuation, and a relatively complete set of clinical assessments and hematology and biochemistry tests. Despite the high doses of levocetirizine administered on a milligram-per-kilogram basis twice daily, its safety profile was similar to that of placebo during 18 months double-masked treatment. Height and body mass increased with increasing age, as expected, in both treatment groups. No adverse effects on development of gross motor skills, fine motor skills, or speech and language skills were noted. Changes in hematology and biochemistry tests were similar in the levocetirizine and placebo treatment groups, and reflected normal development and maturation of body organ function.

Two of the serious adverse effects require detailed comment. Levocetirizine was not implicated in the child who developed acute lymphoblastic leukemia and was discontinued from the study because of this serious event. Indeed, in acute lymphoblastic leukemia cell lines, the first-

Table 5. Laboratory tests: median change from baseline

	Levocetirizine	Placebo
Median change from baseline to end of treatment* (95% two-sided CI)		
Hematology tests		
Hemoglobin (g/l)	4 (2.5; 5.0)	5 (3.5; 6.0)
Hematocrit (fraction of 1)	0.0055 (0.0025; 0.0100)	0.013 (0.0090; 0.0170)
Red blood cell count (10^{12}/l)	−0.04 (−0.085; 0.000)	0.01 (−0.035; 0.050)
Platelet count (10^9/l)	−20 (−34.0; −6.0)	−15.5 (−29.5; −0.5)
White blood cell count† (10^9/l)	−1.15 (−1.60; −0.75)	−1.15 (−1.65; −0.60)
Biochemistry tests		
Aspartate aminotransferase (U/l)	−5.5 (−6.5; −5.0)	−6 (−7.0; −5.0)
Alanine aminotransferase (U/l)	−4.5 (−5.5; −3.5)	−5 (−6.0; −4.0)
Creatinine (μmol/l)	9 (8.0; 10.0)	9.5 (8.5; 10.5)
Bilirubin, total (μmol/l)	0.75 (0.40; 1.10)	0.65 (0.30; 1.05)
Protein, total (g/l)	2 (1.30; 2.50)	2.9 (2.20; 3.60)
C-reactive protein (mg/l)	0 (−1.5; 2.0)	0 (−1.5; 2.0)

*Expected changes with age occurred; all median values were within normal limits for age.

†Expected changes with age also occurred for neutrophil, lymphocyte, eosinophil, monocyte, and basophil counts (not shown).

generation H_1-antihistamine diphenhydramine inhibits clonogenic growth and induces apoptosis, and medications in this class have been postulated to be useful in treating refractory acute lymphoblastic leukemia (7, 8). The relationship of febrile convulsions to study medication was judged to be unlikely by the investigators, and all these children completed the study; however, when the treatment code was broken, they were found to be in the levocetirizine treatment group. The possibility that levocetirizine played a role cannot be conclusively ruled out, and is of considerable interest because in a previous large, 18-month-long study in young atopic children, febrile convulsions were more common in those treated with placebo than in those treated with cetirizine 0.25 mg/kg b.i.d. (5). The latter children had similar exposure to levocetirizine, the active levo-enantiomer of the racemate cetirizine, as the children in the present study did. This issue should be explored further by studying a larger population of young atopic children receiving H_1-antihistamines; for example, by using surveillance prescription-event monitoring or a retrospective cohort study design. Both of these approaches have been used previously to investigate potential H_1-antihistamine adverse effects in older individuals (9, 10).

Levocetirizine is highly selective for the human histamine H_1-receptor, at which it has conformational stability and double the binding affinity of cetirizine. It is eliminated predominantly unchanged in the urine by glomerular filtration. High clearance rates have been documented in young children (11–13) therefore, in this population high levocetirizine doses are needed on a milligram-per-kilogram basis and twice-daily dosing is required. Maturation of renal function is ongoing throughout infancy and early childhood, and by age 4–5 yr, maturation of elimination through the renal route is complete (2). In children age 6–11 yr, renal function is relatively mature, levocetirizine clearance rates are lower than in young children, and H_1-receptor occupancy is high (14, 15); therefore, once-daily dosing is recommended.

Only a few of the more than 40 H_1-antihistamines available worldwide have been studied prospectively during one or more years of regular daily administration (3–6). Such studies are critically important because individuals frequently have several manifestations of allergic disease concurrently, and may use an H_1-antihistamine intermittently or regularly for many years to relieve itching and other symptoms.

H_1-antihistamines are inverse agonists of histamine, a natural body constituent with well-characterized effects in the acute and chronic allergic inflammatory response, and a lesser known but important role in human health through diverse biologic effects in many body systems (3). The older, so-called first-generation H_1-antihistamines that exert their effects through muscarinic, alpha-adrenergic, and serotonin receptors, as well as through H_1-receptors, therefore potentially cause a wide variety of adverse effects, even when administered in recommended doses (3, 4, 16–22). They cross the blood–brain barrier, decrease neurotransmission in the central nervous system, and have the proclivity to cause central nervous system depression evidenced by sedation and impaired cognitive and psychomotor performance. In infants and young children, they potentially cause paradoxical central nervous system stimulation. Older H_1-antihistamines may also cause adverse effects through muscarinic receptors, leading to dry mouth, urinary retention, and sinus tachycardia; and through alpha-adrenergic receptors, leading to hypotension and reflex tachycardia. In addition, some first-generation H_1-antihistamines such as cyproheptadine and ketotifen potentially increase the appetite through antihistamine and/or antiserotonin effects. Even when applied topically to the skin, H_1-antihistamines such as diphenhydramine or promethazine may lead to systemic toxicity (3, 4).

First-generation H_1-antihistamines have been implicated in sudden infant death syndrome, although causality has never been proved (3, 4). After overdose, they potentially cause pupillary dilation, flushed face, tachycardia, respiratory depression, hypotension, seizures, coma, and death (3, 4, 16–22). They are used as sedatives (3, 4, 23, 24), although not necessarily effectively (25); and as appetite stimulants (26) and 'social medications' to control children's behavior (27). Horrifically, they have also been used in homicides of infants and young children (3, 4, 17–19).

The so-called second-generation H_1-antihistamines are considerably safer than their predecessors (3–6, 28–31), although to date there are few prospective studies in infants (28) and few long-term studies of their safety in young children (5, 6). After overdose (30, 31), there are no reports of fatality. Two second-generation H_1-antihistamines, astemizole and terfenadine, have the proclivity to block IKr and other cardiac ion channels, potentially causing prolonged QT interval and ventricular arrhythmia. Consequently, regulatory agency approval for their use has been rescinded in most countries (3, 4).

The study reported here is one of the longest prospective, randomized, double-masked, pla-

cebo-controlled investigations of the safety of any H_1-antihistamine ever conducted in any age group. It confirms the safety of the H_1-antihistamine levocetirizine in young atopic children. In similar populations of young children, the safety of cetirizine has been rigorously documented in an 18 month-long randomized, double-masked, placebo-controlled study (5, 29, 30), and the safety of loratadine has been documented in a 12-month study (6). H_1-antihistamines are frequently used to treat symptoms of allergic rhinitis and urticaria, and as these disorders may recur intermittently or persist over many years, long-term safety studies of additional medications in this class are critically important in the pediatric population.

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