
H₁-antihistamine treatment in young atopic children: effect on urticaria

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Background: There are few published, randomized, double-masked, placebo-controlled, clinical trials of interventions for urticaria in the pediatric population.

Objective: To study the effect of long-term treatment with the H₁-antihistamine levocetirizine on urticaria in young atopic children.

Methods: In the randomized, double-masked, parallel-group Early Prevention of Asthma in Atopic Children Study, children with atopic dermatitis aged 12 to 24 months at enrollment received levocetirizine, 0.125 mg/kg, or matching placebo twice daily for 18 months. On a diary card, the child's caregiver recorded the days on which urticaria was observed. This was validated by the study investigator and entered into the electronic case report form, along with any additional relevant information.

Results: A total of 510 atopic children (mean $\pm$ SEM age, 19.4 $\pm$ 0.2 months) composed the intention-to-treat population. During the subsequent 18 months, 27.5% (70/255) of the children taking levocetirizine and 41.6% (106/255) of the children taking placebo experienced urticaria ($P < .001$). The mean $\pm$ SEM number of urticaria episodes was 0.71 $\pm$ 0.11 in those receiving levocetirizine and 1.71 $\pm$ 0.25 in those receiving placebo ($P < .001$). The mean $\pm$ SEM duration of urticaria episodes was 4.43 $\pm$ 1.57 days in those receiving levocetirizine and 5.36 $\pm$ 1.27 days in those receiving placebo ($P < .001$).

Conclusions: Urticaria is common in atopic toddlers and deserves recognition as an important disorder that occurs early in the atopic marathon. Regular long-term treatment with levocetirizine effectively prevents and treats urticaria in young children. The results of this study strengthen the evidence base for the use of relatively nonsedating, second-generation H₁-antihistamines in the pediatric population.

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INTRODUCTION

During the past decade, understanding of the molecular mechanisms by which H₁-antihistamines interact with histamine H₁-receptors has increased greatly, and it is now known that they do not block these receptors. Rather, all H₁-antihistamines in use function as inverse agonists. They have a preferential affinity for the inactive state of the histamine H₁-receptors. They stabilize the receptors in this conformation, with a shift in equilibrium toward the inactive state and consequent down-regulation of acute and chronic allergic inflammation.^{1,2}

More than 40 different H₁-antihistamines are available worldwide. Although the medications in this class are assumed to be efficacious and safe for urticaria, allergic rhinoconjunctivitis, and other disorders, many of them, particularly the first-generation, sedating H₁-antihistamines, have never been optimally studied in randomized,

double-masked, placebo-controlled, clinical trials in any patient population. The second-generation, relatively non-sedating H₁-antihistamines are well studied compared with the older medications in this class; however, even for these newer medications, there are few long-term studies in individuals of any age, and few studies in young children with urticaria.^{1,3}

Levocetirizine is the active *R*-enantiomer of the racemate cetirizine. It is highly selective for the human histamine H₁-receptor, at which it has twice the binding affinity of cetirizine. Levocetirizine is minimally metabolized, with most of a dose being recovered unchanged in the urine.¹

We hypothesized that in young atopic children, regular treatment with levocetirizine would prevent urticaria episodes and shorten their duration, compared with placebo treatment. We tested this hypothesis in children aged 12 to 24 months who were randomized to treatment with levocetirizine or placebo in the 18-month Early Prevention of Asthma in Atopic Children (EPAAC) Study. The effect of treatment on urticaria was a planned secondary efficacy end point in the EPAAC Study, as specified in the original protocol. The primary end point, efficacy of levocetirizine treatment on preventing or delaying asthma onset in these high-risk atopic children, and other outcomes, including epidemiologic investigations and in-depth levocetirizine safety assessments in this population, will be published separately.⁴

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METHODS

The EPAAC Study protocol was approved by the institutional review board at each of the participating centers in 10 European countries, Australia, and South Africa. Written informed consent was obtained from the child's parent(s) or guardian(s). At screening, the child's history of urticaria, if any, since birth was ascertained and, in children with this history, the age at urticaria onset and provoking factors for urticaria were recorded.

The randomized, double-masked, parallel-group, placebo-controlled, multicenter study was conducted in children with atopic dermatitis, but no asthma or other systemic disease, who had a family history of allergy, were aged 12 to 24 months at study enrollment, and had elevated specific IgE levels to either grass pollen or house dust mite. Assignment to treatment group was made according to preselected randomization factors at baseline, including status of sensitization to grass pollen and house dust mite, sensitization to egg, maternal history of asthma, and country of residence. Severity of atopic dermatitis was evaluated using the modified SCORing Atopic Dermatitis (SCORAD) index.⁵ Urticaria was defined as typical hives or areas of skin swelling, redness, and itching distinctly different from the child's usual inflamed skin lesions of atopic dermatitis. Regular treatment with other H₁-antihistamines was discontinued before study enrollment.

During an 18-month period, 255 children received treatment with levocetirizine, 0.125 mg/kg twice daily, administered as liquid drops,⁶⁻⁸ and 255 children received matching placebo drops twice daily. On diary cards, parent(s) or guardian(s) recorded the days, if any, on which urticaria was observed or on which medication, in addition to the study medication, was given. The urticaria episodes were validated by the study investigators and entered into the electronic case report form during the 8 visits scheduled at regular intervals in the EPAAC Study and the additional visits made as needed. Additional information about other symptoms associated with urticaria or about antecedent events or exposures was recorded, if available.

At each visit, all bottles of medication 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 evaluated by measuring the weight of each bottle returned and subtracting the weight from that of the bottle at the time of dispensing.

In the intention-to-treat population, an urticaria episode was defined as an episode with a date of onset between the date of randomization and the date of the last visit during treatment with levocetirizine or placebo, with both dates included. To correct for different lengths of treatment in different children, the number of episodes of urticaria was extrapolated to 18 months, as follows:

$$\text{number of episodes} = \frac{\text{number of episodes observed}}{\text{length of treatment period in months}} \times 18$$

A similar correction was performed to extrapolate the number of days on which urticaria occurred during 18 months. The number of children with urticaria, the number of episodes of urticaria, and the number of days with urticaria were compared between the children in the levocetirizine treatment group and those in the placebo treatment group.

The number and percentage of children with at least 1 urticaria episode during the 18-month treatment phase were tabulated for each treatment group, overall and in 2 subgroups (those who had *not* experienced urticaria from birth to study enrollment and those who *had* experienced urticaria from birth to study enrollment). The 2 treatment groups were then compared by using a logistic model, including terms for treatment and subgroup of child. The interaction was tested to see if the comparisons between treatment groups (number of children with urticaria, number of days with urticaria, and number of episodes) were affected by whether the children had urticaria before inclusion in the EPAAC Study.

The number of episodes of urticaria and the number of days with urticaria were summarized in the intention-to-treat population for each treatment group overall, and in the 2 subgroups defined previously. The 2 treatment groups were compared using a nonparametric analysis of variance, including terms for treatment and subgroup of child. The interaction between treatment and subgroup of child was also tested.

Differences were considered statistically significant at $P < .05$.

RESULTS

A total of 514 children were randomized to enter the EPAAC Study; 510 children received at least 1 dose of study medication and composed the intention-to-treat population. There were no clinically relevant differences between the 255 children treated with levocetirizine and the 255 children treated with placebo with regard to demographics, duration and severity of atopic dermatitis at study enrollment, and sensitization to allergens (Table 1). Furthermore, there were no clinically relevant differences between the 34.5% (176/510) of the children in the intention-to-treat population who had urticaria during the 18 months of treatment (Table 2) and the intention-to-treat population as a whole (Table 1) with regard to demographics, duration and severity of atopic dermatitis, and sensitization to allergens.

In the intention-to-treat population, during the 18 months of treatment, 27.5% (70/255) of the children receiving levocetirizine experienced urticaria, in contrast to 41.6% (106/255) of the children receiving placebo ($P < .001$) (Fig 1A). The mean $\pm$ SEM number of episodes of urticaria was 0.71 ± 0.11 and 1.71 ± 0.25 in the levocetirizine and placebo groups, respectively ($P < .001$) (Fig 1B). Urticaria was noted on a mean $\pm$ SEM of 4.43 ± 1.57 days in the levocetirizine group and 5.36 ± 1.27 days in the placebo group ($P < .001$) (Fig 1C).

In the intention-to-treat population, 85.9% (219/255) of the children who received levocetirizine and 84.3% (215/255) of the children who received placebo completed 18 months of

Table 1. Description of Children in the Entire Intention-to-Treat Population^a

Variable	Levocetirizine group (n = 255)	Placebo group (n = 255)
Age, mo ^b	19.3 ± 0.3	19.4 ± 0.2
Male sex, %	60.8	64.3
White race, %	88.2	85.1
Duration of atopic dermatitis, mo ^b	15.4 ± 0.5	15.5 ± 0.6
SCORAD index ^{b,c}	29.8 ± 0.8	30.0 ± 0.8
Total IgE level, kU/L ^b	470 ± 94	519 ± 76
Specific IgE level, kU/L ^b		
House dust mite	14.03 ± 1.52	18.79 ± 1.81
Grass pollen	1.45 ± 0.23	1.76 ± 0.47
Cat	2.67 ± 0.58	3.47 ± 0.65
<i>Alternaria</i>	0.59 ± 0.11	0.67 ± 0.12
Cow's milk	5.09 ± 0.99	7.46 ± 1.26
Egg	10.03 ± 1.35	11.15 ± 1.43
Peanut	6.03 ± 1.03	8.49 ± 1.27
Tree mix	1.17 ± 0.30	1.80 ± 0.51

Abbreviation: SCORAD, SCORing Atopic Dermatitis.

^a Data are given as mean ± SEM unless otherwise indicated.

^b At study enrollment.

^c A modified index was used to assess the severity of atopic dermatitis.

Table 2. Description of Children Who Had Urticaria During the 18-Month Treatment Phase^a

Variable	Levocetirizine group (n = 70)	Placebo group (n = 106)
Age, mo ^b	19.0 ± 0.5	19.3 ± 0.4
Male sex, %	54.3	61.3
White race, %	91.4	90.6
Duration of atopic dermatitis, mo ^b	15.8 ± 0.9	16.9 ± 0.8
SCORAD index ^b	30.5 ± 1.7	29.8 ± 1.3
Total IgE level, kU/L ^b	938 ± 306	524 ± 109
Specific IgE level, kU/L ^b		
House dust mite	16.36 ± 3.07	19.23 ± 2.74
Grass pollen	1.33 ± 0.52	0.98 ± 0.15
Cat	3.39 ± 1.52	3.58 ± 1.19
<i>Alternaria</i>	0.83 ± 0.27	0.85 ± 0.27
Cow's milk	7.82 ± 2.35	8.85 ± 2.18
Egg	15.93 ± 3.22	12.57 ± 2.35
Peanut	10.49 ± 2.45	11.31 ± 2.38
Tree mix	1.26 ± 0.38	1.39 ± 0.55

Abbreviation: SCORAD, SCORing Atopic Dermatitis.

^a Data are given as mean ± SEM unless otherwise indicated.

^b At study enrollment.

treatment. In the levocetirizine-treated children, the total daily dose ranged from 2.83 to 3.83 mg. Evaluation of adherence, as reflected in accurate evaluation of study medication intake, was possible for approximately 60% of the chil-

dren and was calculated to be 97.8% in those treated with levocetirizine and 97.0% in those treated with placebo.

In the intention-to-treat population, during the 18 months of treatment, there was no significant difference between the levocetirizine and placebo treatment groups in the amount of other systemic H₁-antihistamines administered as needed for itching in addition to levocetirizine or placebo. In the levocetirizine treatment group, 19.6% (50/255) of the children were given additional systemic H₁-antihistamines, compared with 22.0% (56/255) of those in the placebo group ($P = .55$). The mean ± SEM number of days of use of additional antihistamines was 1.95 ± 0.56 in the levocetirizine treatment group and 3.80 ± 0.91 in the placebo group ($P = .68$).

Of the children in the intention-to-treat population who actually developed hives, 96.0% (169/176) had acute urticaria, by definition lasting 6 weeks or less; of these children, 85.2% (150/176) had hives lasting 7 days or less and 67.6% (119/176) had hives lasting 3 days or less. In 76.7% (135/176) of the children who had urticaria, caregivers related the onset of hives to ingestion of a specific food, including cow's milk (30.1%), egg (27.2%), peanut (16.5%), tree nut (1.9%), fish (1.9%), or other (22.4%). The onset of hives was also reported to be associated with allergen inhalation or contact, medication ingestion, and infection or other provoking factors; however, in some children, the caregivers could not identify a provoking factor.

In the intention-to-treat population, the children who had a history of urticaria before study enrollment were more likely to experience urticaria during the 18-month study, and within this subgroup, levocetirizine significantly reduced the number of children with urticaria, the number of episodes of urticaria, and the number of days with urticaria (Table 3). In contrast, the children who did not have a history of urticaria before study enrollment were less likely to experience urticaria during the 18-month study, and within this subgroup, levocetirizine reduced the number of children with urticaria and the number of episodes of urticaria but not the number of days with urticaria (Table 3).

DISCUSSION

More than one-third of the highly atopic young children in the EPAAC Study had urticaria. In 85.2% of the children with urticaria, the hives lasted 7 days or less, and in 76.7% of the children with urticaria, the hives were associated with food ingestion. Levocetirizine prevented urticaria, as evidenced by a significant decrease in the number of children with urticaria and a significant decrease in the number of episodes of urticaria. It also treated urticaria effectively, as evidenced by a decrease in the duration of episodes.

In infants and young children, acute urticaria (defined as hives of ≤6 weeks' duration)⁹ is considerably more common than chronic urticaria (defined as hives of >6 weeks' duration). This contrasts with older children,⁹⁻¹⁶ in whom chronic urticaria is more frequent and may be associated with physical provoking factors such as cold exposure,^{13,14} or with

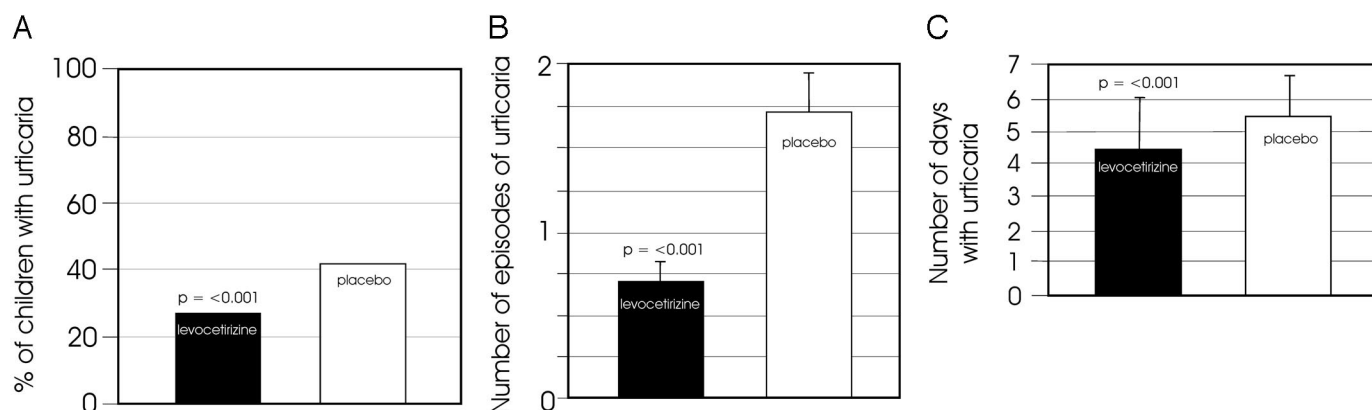


Figure 1. Urticaria in the intention-to-treat population during 18 months of treatment with levocetirizine (n = 255) or placebo (n = 255): percentage of children with urticaria (A), number of episodes of urticaria (B), and number of days with urticaria (C). Data are expressed as mean $\pm$ SEM. The distribution of number of episodes of urticaria and number of days with urticaria was not Gaussian; the statistical comparison between treatment groups was performed using nonparametric methods.

Table 3. Urticaria Data During 18 Months of Treatment With Levocetirizine or Placebo

Variable	No. of children	% of children with urticaria	No. of episodes of urticaria ^{a,b}	No. of days with urticaria ^a
Overall intention-to-treat population ^c				
Levocetirizine group	255	27.5	0.71 $\pm$ 0.11	4.43 $\pm$ 1.57
Placebo group	255	41.6	1.71 $\pm$ 0.25	5.36 $\pm$ 1.27
Those with a history of urticaria at enrollment ^d				
Levocetirizine group	58	50.0	1.18 $\pm$ 0.26	4.10 $\pm$ 1.77
Placebo group	46	80.4	4.61 $\pm$ 1.02	12.40 $\pm$ 4.89
Those without a history of urticaria at enrollment ^e				
Levocetirizine group	197	20.8	0.57 $\pm$ 0.13	4.53 $\pm$ 1.96
Placebo group	209	33.0	1.07 $\pm$ 0.19	3.80 $\pm$ 1.09

^a Data are given as mean $\pm$ SEM.

^b Extrapolated to 18 months.

^c $P < .001$ for the difference between the 2 groups for percentage of children with urticaria, number of episodes of urticaria, and number of days with urticaria.

^d These children had experienced urticaria between birth and inclusion in the Early Prevention of Asthma in Atopic Children (EPAAC) Study. They were among the 12.8% of the 2,184 young atopic children originally screened for the EPAAC Study who had hives between birth and screening.

^e These children had never experienced urticaria before inclusion in the EPAAC Study.

functionally active autoantibodies directed against IgE or the high-affinity IgE receptor.^{15,16}

In a previous randomized, double-masked, 18-month study¹⁷ of young children with atopic dermatitis, acute urticaria was reported in only 5.8% of the children treated with the H₁-antihistamine cetirizine, compared with 16.2% of the placebo-treated children ($P < .001$). This earlier study was conducted in children with less severe atopic dermatitis, some of whom were not sensitized to allergens, and it is, therefore, not directly comparable to the study reported here.

The rationale for administering a levocetirizine dose of 0.125 mg/kg twice daily in the present study was based directly on population pharmacokinetic studies of levocetirizine and on traditional pharmacokinetic and pharmacodynamic studies of levocetirizine performed in children aged 12 to 42 months.^{6–8} In contrast to children aged 7 to 11 years, in

whom levocetirizine pharmacokinetics and receptor occupancy are similar to those found in adults and support once-daily dosing,^{18,19} younger children eliminate levocetirizine relatively rapidly, with oral clearance increasing as body weight and age increase.^{6–8} Therefore, in young children, relatively high doses of levocetirizine and twice-daily dosing are needed.

The administration of an H₁-antihistamine is an important aspect of prevention and treatment of urticaria in children during the early years of the atopic marathon, in addition to other measures that might be indicated, such as avoidance of confirmed specific provoking factors. Recommendations for the use of an H₁-antihistamine to prevent and treat urticaria in young children are mostly based on evidence obtained from short-term clinical trials in older children and adults^{1,3} and on clinical experience. The results of this study strengthen the

evidence base for the use of relatively nonsedating, second-generation H₁-antihistamines in the prevention and treatment of urticaria in young children.

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