

Short communication

Loratadine in the treatment of mosquito-bite-sensitive children

Background: Children frequently experience harmful whealing and delayed papules from mosquito bites. Whealing is mediated by antiallergic IgE antibodies and histamine, but the effect of antihistamines on mosquito-bite symptoms has not been evaluated in children.

Methods: The effect of loratadine (0.3 mg/kg) was examined in 28 mosquito-bite-sensitive children (aged 2–11 years). The double-blind, placebo-controlled, crossover study was performed with exposure to *Aedes aegypti* laboratory mosquitoes. The size of the bite lesion and the intensity of pruritus (visual analog scale) were measured at 15 min and at 2, 6, and 24 h.

Results: Loratadine decreased the size of the wheals by 45% ($P < 0.001$, 25 children) and accompanying pruritus by 78% ($P = 0.011$, 12 children) at 15 min compared to placebo. The size of the 24-h delayed bite lesion also decreased significantly ($P = 0.004$), but there was no change at 2 or 6 h. Loratadine was well tolerated and no marked side-effects were recorded.

Conclusions: This study in children shows that prophylactically given loratadine decreases significantly the whealing and pruritus caused by mosquito bites and also reduces the size of the 24-h bite lesions. Therefore, the therapeutic profile of loratadine extends from immediate to delayed allergic symptoms in mosquito-bite-sensitive children.

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Mosquitoes frequently cause harmful bite reactions such as immediate wheals and delayed bite papules in children and adults. People exposed for the first time to the bites of a certain mosquito species are first non-reactive, but after repeated bites they become sensitized (1–3). At present, it is well documented that whealing is mediated by antiallergic IgE antibodies (4–7). It is also known that mosquito saliva may contain species-specific and species-shared antigens (8–9). The delayed papules developing after mosquito bites are accompanied by influx of eosinophils and lymphocytes (10), but whether these lesions represent late-phase type I or cell-mediated type IV reactions, or both, is not known.

Children in different parts of the world are frequently sensitized to *Aedes* mosquitoes (11). In southern Finland, almost all children react to *A. communis* bites, and the size of the wheal correlates with the antiallergic IgE antibody levels (12). The antihistamines cetirizine and ebastine have been shown to decrease whealing and accompanying pruritus in mosquito-bite-sensitive adults (13–15), but no studies exist in children. Therefore, we performed a placebo-controlled, cross-

over study to determine whether the antihistamine loratadine has an effect on the mosquito-bite symptoms in children.

Material and methods

Patients

Twenty-eight mosquito-bite-sensitive children (mean age 7.2 years, range 2–11 years) were included in the study. All children had experienced harmful mosquito-bite reactions and had been admitted to the Tampere University Hospital or to the Hospital for Skin and Allergic Diseases in Helsinki. The study was performed in March–October 1999. At inclusion, all children were challenged with a bite of *A. aegypti* laboratory mosquitoes (11). In 16 children, the diameter of the bite reaction was 5 mm or bigger both at 15 min and at 24 h, in nine children only at 15 min, and in three children at 24 h. In addition, all subjects had a positive (> 3 mm) skin prick test reaction to the histamine dihydrochloride (10 mg/ml; ALK a/s, Hørsholm,

Denmark). Four children had a history of an atopic disorder (atopic dermatitis, allergic rhinitis, or asthma). In the 28 children, the total IgE level was 407 kU/l (mean; range 6–3535 kU/l); in 19 children, the level was increased; i.e., it was above the reference level of the corresponding age group.

The study was approved by the ethics committees of both hospitals, and informed consent was obtained from all parents and also from the 13 children who were over 7 years of age.

Loratadine

The study was a double-blind, crossover study with 0.3 mg/kg of loratadine (1 mg/ml mixture in 120-ml bottles) and an identical placebo mixture. The drugs were taken from the bottles with a 5-ml syringe and were given daily at 8 a.m. for 4 days. The drug periods were separated by a 3-day washout period, and the next mosquito challenge was performed 6 days after the end of the previous drug period. The children visited the investigators on days 3 and 4, and any adverse event was recorded during both visits.

Mosquito exposure

The *A. aegypti* bite exposure was performed between noon and 3 p.m. on day 3. One mosquito was allowed to feed on the right (week 1) and left (week 2) forearms. The size of the bite reaction was measured (two perpendicular diameters in mm) at 15 min and at 2, 6, and 24 h. The measurements at 15 min and 24 h were performed by the investigators, and at 2 and 6 h by the parents. Twelve children (age 7 years or older) evaluated pruritus with a 100-mm visual analog scale (VAS) ranging from 0 (no pruritus) to 100 (very intense pruritus).

Statistical analysis

Wilcoxon's signed rank test with exact *P* value was used to detect significant differences between loratadine and

placebo treatments at 15 min and at 2, 6, and 24 h. The sum of these four measurements was also analyzed. A *P* value below 0.05 was considered significant.

Results

Twenty-five of the 28 children completed the study according to the protocol. Of the 25 children, 12 received loratadine in the first and 13 in the second week. Three children dropped out in the first trial week, and they all had received placebo. One child considered the taste of the mixture too unpleasant, the parent of one child forgot once to give the drug, and the third child could not be exposed because no mosquitoes were alive.

Effect of loratadine on the size of mosquito-bite lesions

Loratadine decreased significantly the size of the bite lesion at 15 min ($P < 0.001$) and at 24 h ($P = 0.004$) compared to placebo (Table 1). The median size of the bite lesion decreased by 45% (from 64 to 35 mm²) at 15 min and by 27% (from 49 to 36 mm²) at 24 h. Loratadine had no significant effect on the size of the bite lesion at 2 and 6 h. When all four time points were pooled, the median size of the bite lesion had decreased by 32% (from 53 to 36 mm²), which is a significant change ($P = 0.01$; Table 1).

Twenty-one of the 25 children had a smaller bite lesion on loratadine than on placebo at 15 min, and 18 children when the sizes of the bite lesions at all four time points were combined. The effect of loratadine was the same whether the lesions were large or small (Fig. 1).

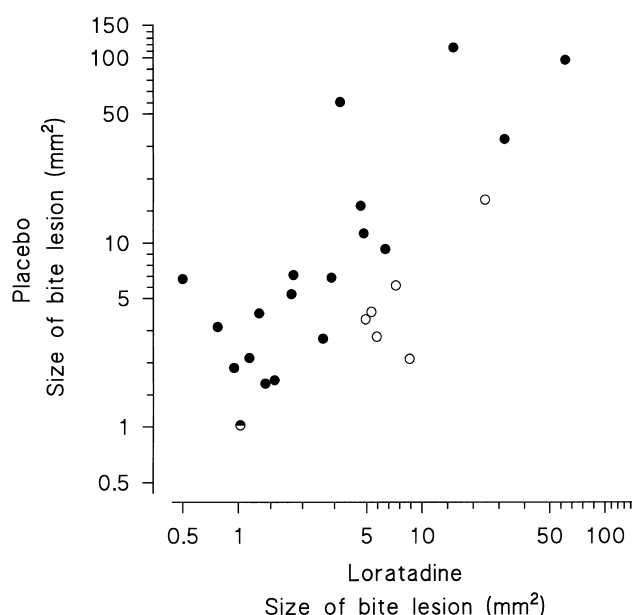


Figure 1. Size of bite lesion in 25 mosquito-bite-sensitive children. Size is sum of measurements performed at 15 min, and at 2, 6, and 24 h. Eighteen children had smaller bite lesion on loratadine (closed circles) than on placebo (open circles) treatment.

Table 1. Effect of loratadine on mosquito bites in 25 children

	Treatments		<i>P</i> value
	Loratadine Median (range)	Placebo Median (range)	
Size of bite lesion (mm ²)			
15 min	35 (6, 120)	64 (9, 400)	<0.001
2 h	16 (0, 288)	15 (0, 840)	0.53
6 h	9 (0, 625)	20 (0, 1360)	0.14
24 h	36 (0, 1600)	49 (16, 2500)	0.004
All four time points	36 (5, 610)	53 (10, 1135)	0.01
Pruritus at 15 min*	10 (0, 75)	45 (0, 90)	0.011

* Visual analog scale ($n = 12$).

Effect of loratadine on mosquito-bite pruritus

Pruritus associated with bite lesions was measured in 12 children. At 15 min, the median VAS decreased by 78%; i.e., from 45 on the placebo to 10 on the loratadine treatment ($P=0.011$; Table 1). At other time points, the pruritus was very weak, the VAS scores ranging from 8 to 3. Therefore, no statistical comparisons could be performed.

Side-effects

Gastrointestinal symptoms were reported during loratadine treatment in two children. One child experienced mild abdominal pain after taking the drug on all four days, and another child had moderate diarrhea and nausea during two days of the treatment. No other side-effects were recorded either on loratadine or on placebo.

Discussion

The present placebo-controlled, crossover study in 25 mosquito-bite-sensitive children showed that prophylactically given loratadine 0.3 mg/kg had a significant effect on the immediate symptoms and on the 24-h bite papules caused by *A. aegypti* laboratory mosquitoes. To our knowledge, no previous controlled trials have been performed with antihistamines in mosquito-bite-sensitive children. The results on the effect of loratadine in whealing and accompanying pruritus caused by *A. aegypti* mosquito bites are in agreement with our previous placebo-controlled studies in mosquito-bite-sensitive adults. These trials performed either in the laboratory or in the field showed that both cetirizine 10 mg and ebastine 10 or 20 mg decreased whealing by 30–40% and accompanying pruritus by 70–80% (14–16). The marked effect of antihistamines on the immediate mosquito-bite symptoms is not unexpected. Previous studies have shown that mosquito-bite-sensitive subjects frequently have antisaliva IgE antibodies (4, 9, 11, 12), that whealing can be passively transferred with antisaliva IgE antibodies (5), and, finally, that histamine is released into the skin during whealing (7).

Interestingly, in the present children, loratadine also decreased significantly the size of the delayed 24-h bite reaction. Previously, we found a similar effect with cetirizine 10 mg (14) and suggested that the delayed mosquito bite lesions could be late-phase type I allergic reactions. In agreement with this, the development of the delayed bite papules is characterized by early influx of eosinophils and neutrophils, and subsequent increase of CD4+ lymphocytes (10). However, in the same study, we found that the numbers of eosinophils and T cells in these mosquito-bite lesions were higher during cetirizine than placebo treatment. Studies with intra-dermal injections of pollen or house-dust mite antigens have also shown that cetirizine seems not to inhibit the late-phase cellular inflammatory responses in the skin (17, 18). Skin chamber examinations in pollen-allergic subjects have also shown that loratadine does not inhibit the late-phase reaction after 2 h (19). Therefore, the mechanism by which cetirizine and loratadine decrease the size of the delayed 24-h mosquito-bite lesions remains a subject for further examinations.

In the present study, we exposed the children to *A. aegypti* laboratory mosquitoes although they had not been in contact with this tropical and subtropical species. The children in Finland have, however, been sensitized in the field to *A. communis*, a species which has cross-reacting saliva antigens with *A. aegypti* (8, 12). Our studies in the Finnish mosquito-bite-sensitive adults have shown that the bite reactions are more intense to a native species, i.e., *A. communis*, than to a laboratory species, i.e., *A. aegypti* (2). In adults, the effect of both cetirizine and ebastine has been shown to be good on the large bite reactions received from the local mosquitoes in the field (14, 16). For this reason, we believe that loratadine would also give significant relief from the symptoms in mosquito-bite-sensitive children if they were bitten in the field by local mosquitoes.

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