

Short communication

Comparison of cetirizine, ebastine and loratadine in the treatment of immediate mosquito-bite allergy

Background: People frequently experience whealing and delayed papules from mosquito bites. Whealing is mediated by antiserum immunoglobulin (Ig)E antibodies and histamine. Cetirizine, ebastine and loratadine have earlier shown effects on mosquito-bite reactions but no comparative studies exist.

Methods: A double-blind, placebo-controlled, cross-over study was performed with cetirizine 10 mg, ebastine 10 mg and loratadine 10 mg in 29 mosquito-bite-sensitive adults exposed to *Aedes aegypti* mosquito-bites. The size of the bite lesion and the intensity of pruritus (visual analog scale) were measured at 15 min and 2, 6 and 24 h.

Results: Cetirizine and ebastine, but not loratadine, decreased significantly the size of whealing ($P < 0.01$) and accompanying pruritus ($P < 0.001$) compared to placebo. Cetirizine was most effective on pruritus but caused more often sedation than ebastine or loratadine. The delayed bite symptoms remained too faint for any statistical comparison.

Conclusion: This comparative study in mosquito-bite-sensitive adults shows that cetirizine and ebastine decrease significantly whealing and accompanying pruritus, and that cetirizine seems to be the most effective against pruritus.

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People frequently get pruritic bite reactions such as immediate wheals and delayed bite papules from mosquito bites. Sensitization to mosquito bites occurs commonly in childhood, and bite reactivity often persists for years (1). Mosquito-bite whealing is mediated by antiserum IgE antibodies and histamine (2–5). The bite reactions are usually more intense at the onset of the mosquito season, and people are also known to get harmful reactions when exposed to foreign mosquito species while travelling (6).

Treatment of mosquito bites with topical antihistamines or other preparations has given variable results in controlled studies (7, 8). In contrast, oral antihistamines, cetirizine and ebastine, have been shown to decrease whealing and accompanying pruritus and have an effect on the delayed bite symptoms in adults exposed to mosquitoes in the laboratory or in the field (9–11). One study in mosquito-bite-sensitive children showed that loratadine also had an effect on immediate pruritus (12). The effects of the different antihistamines have, however, not been evaluated in a single study. We therefore performed a placebo-controlled, cross-over study with cetirizine, ebastine and loratadine on adult mosquito-bite sensitive subjects.

Material and methods

Patients

Twenty-nine mosquito-bite-sensitive adult subjects (mean age 39 years, range 26–61 years) volunteered for the study. They were Tampere and Helsinki University Hospitals staff. All subjects had experienced harmful mosquito-bite reactions in the field and had been previously challenged with *A. aegypti* laboratory mosquitoes. All subjects suffered from at least 5 mm diameter immediate and/or delayed 24 h bite reaction and additionally all reacted to histamine dihydrochloride (10 mg/ml) prick test control. Seven subjects had a history of atopic dermatitis syndrome, allergic rhinitis or asthma.

The study was approved by the Ethics Committees of the two hospitals, and an informed consent was obtained from all subjects.

Study protocol and antihistamine administration

The study period was 4 weeks for each subject and included two visits per week with the investigator. The study was performed in a double-blind, cross-over manner with cetirizine 10 mg, ebastine 10 mg, loratadine 10 mg and placebo capsules. Each drug was taken daily at 8 AM for 4 days followed by 3 days without any drugs. Mosquito challenge was performed on day 3 in each drug period, i.e., 7 days after the previous challenge. Any adverse events were recorded during the study.

Mosquito-bite exposure

The bite exposure was performed with *A. aegypti* laboratory mosquitoes between noon and 3 PM. One mosquito in a cage was allowed to feed on the right or left forearm, weeks 1 and 3 or weeks 2 and 4, respectively. The size of the bite reaction was measured (two perpendicular diameters in mm) at 15 min and 2, 6 and 24 h. Measurements at 15 min and 24 h were performed by the investigators, and at 2 and 6 h by the subjects. Pruritus was evaluated using a 100-mm visual analog scale (VAS) ranging from 0 (no pruritus) to 100 (very intense pruritus).

Statistics

Comparison between each antihistamine and placebo was made using Wilcoxon's signed rank test with Hommel's adjusted *P*-value (13). Comparison between the effects of the three antihistamines was performed with Friedman's two-way analysis of variance by ranks with an exact *P*-value. The size of the 15 min bite reaction in the inclusion phase and in the placebo treatment period was compared by determining the concordance correlation coefficient for agreement (14).

Results

All 29 subjects completed the study according to the protocol. Two subjects were, however, excluded from the final analysis owing to negative bite reactions during the placebo treatment. In the remaining 27 subjects, the correlation coefficient between the size of the wheal in the inclusion phase and placebo treatment period was good, i.e., 0.59 (95% confidence intervals 0.32–0.86).

In the remaining 27 subjects the size of the bite reaction was small during the placebo treatment at 2 h (median size 9 mm²), 6 h (median 4 mm²) and 24 h (median 9 mm²), and pruritus was also very faint or absent in most subjects. Therefore, no significant effects could be expected by any of the antihistamines on the delayed bite symptoms and the results are not presented in more detail.

Effect of cetirizine, ebastine and loratadine on mosquito-bite whealing

At 15 min, cetirizine 10 mg (*P*=0.003) and ebastine 10 mg (*P*=0.003), but not loratadine 10 mg (*P*=0.09), decreased significantly the size of the 15 min bite reaction compared to the placebo (Table 1). Cetirizine was better than placebo in 15 and ebastine in 18 subjects, and it seems that the antihistamines had a more profound effect on the bigger than on the smaller

wheals (Fig. 1). The differences between the effects of the three antihistamines on whealing were not significant (*P*=0.19; Table 1).

Effect of cetirizine, ebastine and loratadine on pruritus

Cetirizine and ebastine, but not loratadine (*P*=0.067), decreased significantly (*P*<0.001) pruritus at 15 min compared to the placebo (Table 1). Cetirizine was more effective than placebo in 22, ebastine in 21 and loratadine in 16 subjects. Comparison of the effects of the three antihistamines on pruritus at 15 min ranked cetirizine better than ebastine and ebastine better than loratadine (*P*<0.001; Table 1)

Sedation

Fourteen (52%) subjects reported sedation, and in two subjects this occurred during three and in another two subjects during two-drug periods. Eight subjects experienced sedation during cetirizine, five during loratadine, four during placebo and two during ebastine treatment (Fig. 2). Sedation ranged from mild to severe but it caused no drop-outs. No other adverse events were recorded.

Discussion

The present placebo-controlled, cross-over study in 27 mosquito-bite-sensitive subjects showed that prophylactically given cetirizine 10 mg and ebastine 10 mg daily had a significant effect on whealing and pruritus caused by *Aedes aegypti* laboratory mosquitoes. This finding is in agreement with our previous placebo-controlled studies in mosquito-bite-sensitive adults. Those trials, performed either in the laboratory with *A. aegypti* or in the field with *A. communis* mosquitoes, showed that both cetirizine 10 mg and ebastine 10 mg decreased whealing by 30–40% and accompanying pruritus by 70–80% (9–11). The marked effect of these two antihistamines is not unexpected because mosquito-bite whealing is a type I allergic reaction mediated by IgE antisaliva antibodies and histamine (1–3, 15). In the present study, loratadine 10 mg, however, did not show any significant effect compared to placebo on the whealing or on pruritus. This result is contrary to our previous placebo-controlled study in mosquito-bite-sensitive children (12). In that trial we

Table 1 Size of the bite lesion and pruritus at 15 min after *Aedes aegypti* mosquito bites in 27 mosquito-bite-sensitive subjects

	Placebo	Antihistamines			<i>P</i> -value between antihistamines†
		Cetirizine	Ebastine	Loratadine	
Size of bite lesion (mm ²)	28 (16, 63)‡	25 (12, 25)*	16 (12, 25)*	25 (16, 48)	0.190
Pruritus (visual analogue scale)	50 (10, 70)	0 (0, 30)**	10 (0, 30)**	30 (10, 60)	0.001

† Friedman two-way analysis of variance by ranks, ‡ Median (IQR), **P*<0.01, ***P*<0.001; difference between antihistamine and placebo (Wilcoxon's Signed Rank Test with Hommel's adjusted *P*-value).

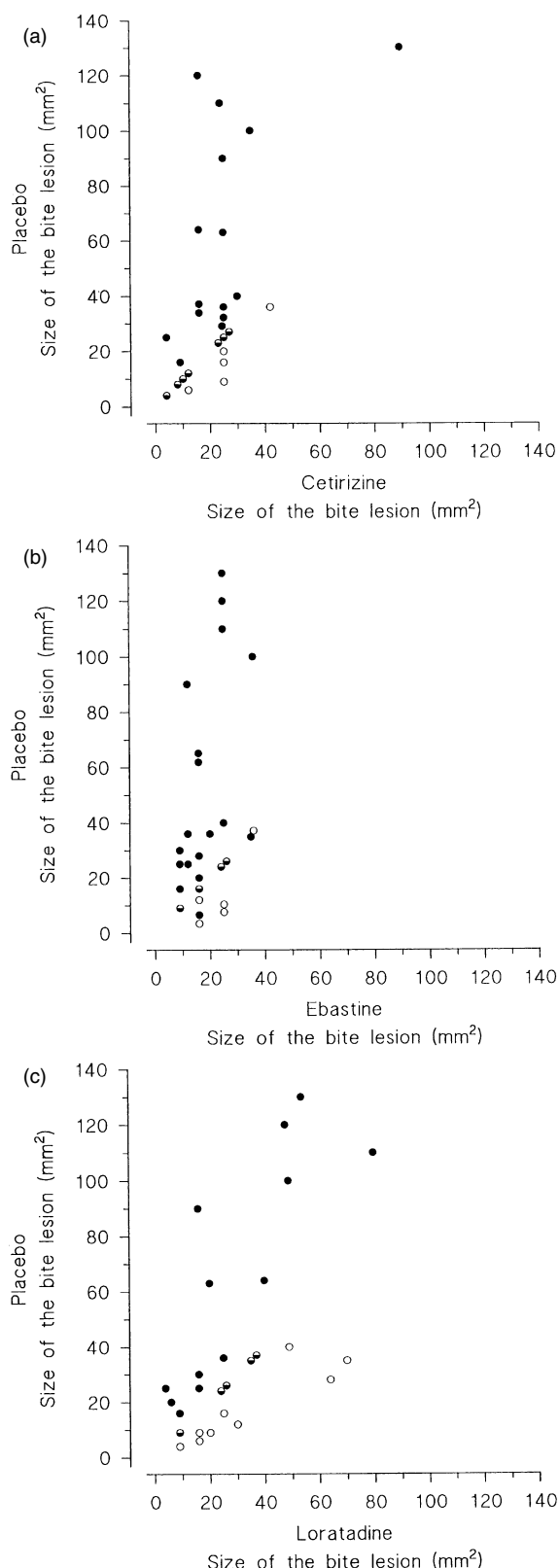


Figure 1. Size of the 15 min wheal in 27 mosquito-bite-sensitive adults during the treatment with cetirizine 10 mg (A), ebastine 10 mg (B) and loratadine 10 mg (C) compared to the placebo. Antihistamine was more effective than placebo (•) in most subjects whereas in a few subjects the placebo was more effective than the antihistamine (○).

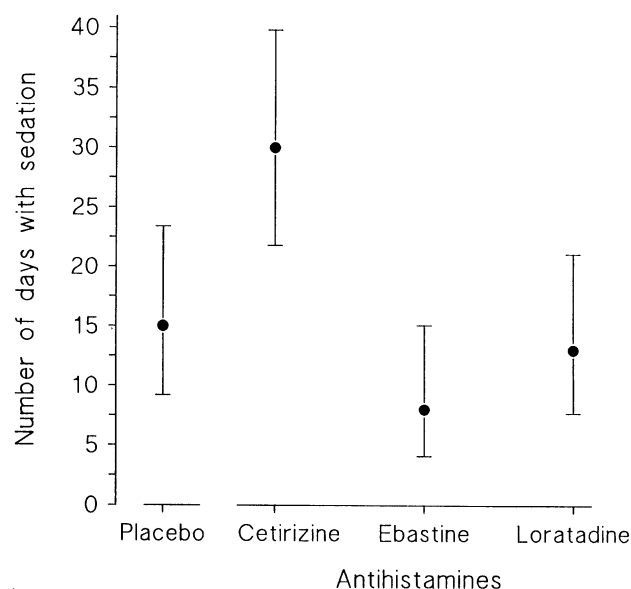


Figure 2. Number of days with sedation and 95% confidence intervals during the treatment of 27 mosquito-bite-sensitive adults with placebo, cetirizine 10 mg, ebastine 10 mg and loratadine 10 mg. During the trial sedation was observed during a total of 108 days for each drug.

gave loratadine 0.3 mg/kg daily to children, and the whealing decreased by 45% and the accompanying pruritus by 78%. The reason for the nonsignificant result in the present study in adults could be the dose of loratadine, 10 mg daily, which equals to 0.14 mg/kg for a 70 kg person. We assume that a higher loratadine dose, e.g., 20 mg daily, would have given significant effects compared to placebo on the immediate symptoms caused by mosquito bites.

Statistical comparison between the antihistamines showed that cetirizine had a more profound effect on mosquito-bite pruritus than ebastine. This could be of clinical importance because the relief of the itch is important for mosquito-bite-sensitive subjects who often suffer from the bites throughout the mosquito season (6). Sedation is also of clinical importance when considering the effects of second generation antihistamines. In the present 4-week study, as many as half of the subjects, reported sedation. Eight subjects experienced sedation during cetirizine, five during loratadine, four during placebo and two during ebastine treatment. There are different opinions whether cetirizine causes more sedation than the other selective histamine H1 antagonists (16–18). Possible sedation from cetirizine or other antihistamines seems, however, not to be any significant problem in the treatment of mosquito-bite reactions because no drop-outs occurred in the present laboratory study or in our previous studies performed with cetirizine or ebastine in the field (9, 10). When the mosquito-bite-sensitive subjects notice that an antihistamine really alleviates their symptoms, they will obviously tolerate the sedation as long as it remains mild.

In conclusion, the present comparative study performed in adult mosquito-bite-sensitive subjects showed that cetirizine and ebastine, but not loratadine, have a similar effect on mosquito-bite whealing, and that the accompanying pruritus relieved somewhat better with cetirizine than with ebastine. A further comparative study is warranted to show whether the antihistamines studied have different efficacy profiles on delayed mosquito-bite reactions.

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