

Treatment of Mosquito Bites with Ebastine: A Field Trial

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Wealing and pruritic, long-lasting papules are a common nuisance from mosquito bites. Antihistamines can be expected to decrease wealing, but their effect on the delayed bite symptoms needs to be elucidated. We studied the effect of ebastine in 28 mosquito-bite sensitive adult subjects exposed to *Aedes communis* bites in the field. Ebastine 20 mg and placebo were given for 4 days in a cross-over fashion, and the size of the bite lesion and the intensity of pruritus (visual analogue scale) were measured at 15 min and 2, 6 and 24 h after the bites. Ebastine decreased significantly ($p < 0.001$) the size of the bite lesion and pruritus at 15 min. Ebastine also had a significant effect ($p < 0.01$) on pruritus at 2 and 24 h, and this effect was highly significant when the measurements at all 4 time points were pooled. Five patients (18%) on ebastine, but none on placebo, experienced sedation (ns). The present field study shows that ebastine 20 mg given prophylactically is effective against immediate mosquito bite symptoms, and that it also significantly decreases pruritus associated with the delayed bite papules. **Key words:** antihistamines; mosquito-bite allergy; wealing; pruritus

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Mosquito bites cause wealing and delayed bite papules in most people, especially at the onset of the mosquito season (1, 2). Several mosquito saliva allergens have been characterized and the immediate bite reaction is mediated by anti-saliva IgE antibodies and histamine (3–6). Delayed bite lesions consist of eosinophils and lymphocytes, but the exact pathomechanism is not known (7).

Cetirizine antihistamine has been shown to decrease pruritus, wealing and the size of bite papules caused by mosquito bites received in the laboratory or in the field (8, 9). We showed previously that ebastine was effective against immediate bite reactions caused by *Aedes aegypti* laboratory mosquitoes (10). In the present placebo-controlled, cross-over study we examined the effect of ebastine on the reactions to *Aedes communis* bites received in the field.

MATERIAL AND METHODS

Subjects

Twenty-eight mosquito-allergic subjects, 24 females and 4 males (mean age 40 years, range 18–58 years), volunteered for the study. The subjects were patients or personnel of the Departments of Dermatology, Tampere University Hospital and Helsinki University Central Hospital. All 28 subjects were challenged with *Aedes aegypti* laboratory mosquitoes as described previously (7), and the diameter of the bite reaction was at least 5 mm at 15 min and/or at 24 h. In

addition, all subjects had a positive (>3 mm diameter) prick test reaction to histamine dihydrochloride (10 mg/ml; ALK a/s, Copenhagen, Denmark).

The mean total IgE level of the patients was 82.5 kU/l (range 0–552 kU/l). Four subjects had increased total IgE levels (>130 kU/l) and a history of atopic disorder. The study was approved by the Ethics Committees of the hospitals, and informed consent was obtained before the study.

Ebastine dosage and observation of side-effects

The study was a double-blind, cross-over study with 20 mg of ebastine in 10 mg capsules and identical placebo capsules. The drugs were given daily at 08.00 a.m. for 4 days. The drug periods were separated by a 3-day wash-out period. The subjects visited the investigators on days 3 and 4 in both drug periods and were evaluated for bite reactions and adverse events.

Mosquito exposure and measurement of bite reactions

The study was performed during the mosquito season in June–August 1998. The mosquito bite exposure was performed between 12.00 a.m. and 15.00 p.m. on day 3 of the 2 treatment periods. The exposure took place in the field near the respective hospitals, where 90% of the mosquitoes belong to the *Aedes communis* species (11). One to 3 mosquitoes were allowed to feed on the forearm; thereafter 1 bite was marked by the investigator.

The size of the bite reaction in square millimetres was obtained by measuring 2 perpendicular diameters in millimetres. Pruritus was evaluated on a 100-mm visual analogue scale (VAS). At 15 min and 24 h the measurements were performed by the investigators, at 2 h and 6 h by the subjects.

Statistical analysis

Wilcoxon's signed rank test with exact p value was used for detecting the significance between ebastine and placebo treatments at 15 min and 2, 6 and 24 h. The sum of these four measurements was also analysed. Correlations were estimated by Spearman's correlation coefficient method. McNemar test using binomial distribution with exact p value was used to analyse side-effects. For all statistical tests significance was defined as $p < 0.05$.

RESULTS

All 28 subjects received *Aedes communis* bites in the field according to the protocol, and both drug periods were completed without any drop-outs.

Effect of ebastine on the size of mosquito bite lesions

Ebastine significantly decreased ($p < 0.001$) the size of the bite lesion at 15 min compared with placebo (Table I). The median size of the bite lesion decreased by 67% from 49 mm² to 16 mm². Ebastine caused no significant decrease in the size of the bite lesion at 2, 6 and 24 h.

Table I. Effect of ebastine 20 mg on the mosquito bites received in the field in 28 mosquito-allergic subjects

Measurements	Treatment		p-value
	Ebastine Median (range)	Placebo Median (range)	
Size of the bite lesion (mm ²)			
15 min	16 (0, 104)	49 (0, 195)	<0.001
2 h	25 (0, 450)	30 (0, 400)	0.63
6 h	16 (0, 2304)	25 (0, 2000)	0.41
24 h	25 (1, 1800)	36 (1, 500)	0.79
All 4 time points	30 (3, 1164)	53 (6, 698)	0.67
Pruritus (visual analogue scale) (mm)			
15 min	20 (0, 90)	75 (0, 100)	<0.001
2 h	0 (0, 50)	20 (0, 80)	0.0011
6 h	0 (0, 50)	0 (0, 70)	0.83
24 h	0 (0, 50)	5 (0, 80)	0.011
All 4 time points	10 (0, 50)	25 (0, 75)	<0.001

Effect of ebastine on the mosquito bite pruritus

Ebastine had a significant effect on pruritus at 15 min ($p < 0.001$), 2 h ($p = 0.0011$) and 24 h ($p = 0.011$) (Table I). At 15 min, median VAS decreased by 73% from 75 to 20, at 2 h by 100% from 20 to 0 and at 24 h by 100% from 5 to 0.

When pruritus was analysed at all 4 time points, the effect of ebastine was also significant ($p < 0.001$; Table I). Twenty-five of the 28 subjects had less pruritus on ebastine than on placebo treatment, and the decrease in pruritus occurred similarly in the subjects with high or low VAS scores (Fig. 1).

Side-effects

Five patients (18%) reported mild to severe sedation during the study, whereas no sedation was observed during placebo ($p = 0.063$). No other side-effects were observed during the study.

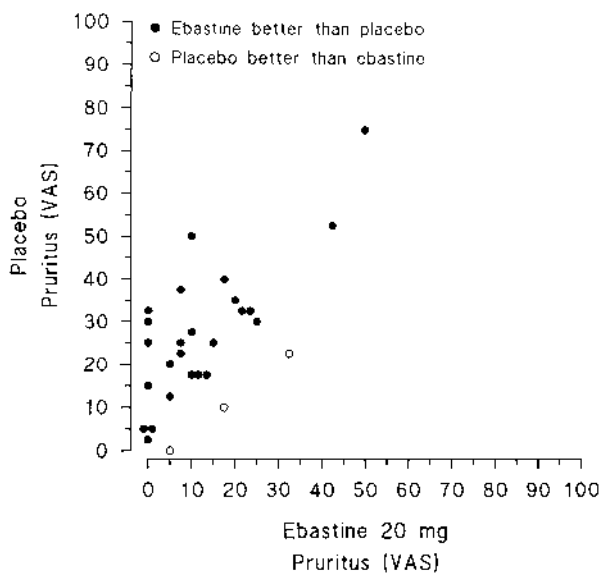


Fig. 1. Comparison of the effects of ebastine 20 mg and placebo on pruritus at all 4 time points, i.e. at 15 min, 2 h, 6 h and 24 h, after *Aedes communis* bites in 28 mosquito bite-sensitive subjects. Ebastine was better than placebo in 25 subjects and the effect was seen both on the patients with intense and less intense pruritus. VAS = visual analogue scale.

DISCUSSION

This placebo-controlled, cross-over study in 28 mosquito bite-sensitive subjects showed that prophylactically given ebastine 20 mg had a significant effect on the immediate symptoms caused by *Aedes communis* mosquito bites in the field. This is in agreement with our findings of the effect of ebastine 10 mg or 20 mg on the *Aedes aegypti* laboratory mosquito bites (10). Our previous study with cetirizine 10 mg in the field also showed a marked decrease in the immediate symptoms in 18 mosquito-bite sensitive subjects (9). From these 2 studies performed similarly in the field, it can be concluded that ebastine 20 mg decreases mosquito-bite wealing 67% and cetirizine 10 mg 42%, and both antihistamines decrease accompanying pruritus as much as 70%.

In the present study, ebastine decreased significantly also pruritus at 2 and 24 h, although we did not find a similar effect in our previous study with *Aedes aegypti* laboratory mosquitoes (10). The reason for this is the fact that in the present study the delayed bite reactions were markedly more intense after the *Aedes communis* bites in the field than those received from the laboratory mosquitoes in our previous study. Although ebastine 20 mg decreased significantly pruritus in the present study, it had no marked effect on the size of the delayed bite lesions. One reason for this could be that the size of the delayed bite lesion is influenced by other mediators in addition to histamine release. In our previous microdialysis study we found leukotriene release 1–4 h after the bites, but no data on leukotriene or histamine activity is available from the 24-h bite lesions (5). In contrast to the present study, it was previously shown that cetirizine 10 mg reduced the size of the 24-h bite lesions (10). In both studies the *Aedes communis* bite exposures took place in the same way in the field and the mosquito-bite sensitive subjects were similarly collected. It should be remembered, however, that direct comparison between the effects of cetirizine and ebastine on the size of the mosquito-bite lesions would be possible only by using these drugs in the same trial. In addition to direct comparison, it would be interesting to know whether ebastine has a similar effect on the influx of eosinophils and T lymphocytes in mosquito-bite lesions as that reported for cetirizine (7).

Sedation can also be experienced with newer antihistamines (12). In the present study with ebastine 20 mg, sedation was

unexpectedly reported by 5 subjects during ebastine and in none during placebo treatment, a difference which did not reach statistical significance. Our previous mosquito bite study with ebastine 10 mg or 20 mg showed no significant difference in sedation between ebastine and placebo treatments (10).

We conclude that ebastine is a useful drug for mosquito-sensitive subjects, especially when they suffer from immediate bite symptoms or long-lasting pruritus.

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