Acta Derm Venereol (Stockh) 1997; 77: 315–316

Effect of Ebastine on Mosquito Bites

T. REUNALA[1], H. BRUMMER-KORVENKONTIO[2], L. PETMAN[1], T. PALOSUO[2] and S. SARNA[3]

[1]*Department of Dermatology, University of Helsinki and University Hospital for Skin and Allergic Diseases,* [2]*National Public Health Institute and* [3]*Department of Public Health, University of Helsinki, Helsinki, Finland*

Mosquito bites usually cause wealing and delayed bite papules. Cetirizine decreases wealing, bite papules and pruritus but the effect of other antihistamines on mosquito bites is unknown. We studied the effect of ebastine in 30 mosquito bite-sensitive adult subjects. Ebastine 10 mg or 20 mg and placebo were given for 4 days in a cross-over fashion. *Aedes aegypti* bites were given on forearms. The size of the bite lesions and pruritus (visual analogue score) were measured at 15 min, 2, 6, and 24 h after the bites.

Twenty-five subjects were evaluable in the study. At 15 min ebastine decreased significantly the size of the bite lesion ($p = 0.0017$) and pruritus ($p < 0.0001$). The effects of 10 mg and 20 mg of ebastine were similar. No significant effect was found at 2, 6 or 24 h, but when the measurements at all four time points were compiled the size of the bite lesion and pruritus score decreased significantly. Sedation occurred during ebastine treatment in 6 (21%) and during placebo treatment in 2 (7%) subjects. The present results show that prophylactically given ebastine is effective against immediate mosquito bite symptoms.

Key words: antihistamines; wealing; pruritus; mosquito allergy.

(Accepted January 15, 1997.)

Acta Derm Venereol (Stockh) 1997; 77: 315–316.

T. Reunala, MD, University Hospital for Skin and Allergic Diseases, FIN-00250 Helsinki, Finland.

Mosquito bites usually cause cutaneous bite reactions, which include immediate weals and delayed bite papules. In Finland about 10% of the population experience abnormally large bite lesions during the mosquito season (1). The immediate mosquito bite reaction is mediated by antisaliva IgE antibodies and histamine, but the mechanism leading to the delayed bite papules is unknown (2, 3). Previous placebo-controlled studies performed in the field in Finland showed that prophylactically given cetirizine 10 mg, a non-sedative anti-H1-antihistamine, was effective against mosquito bite reactions both in adult volunteers and in subjects abnormally sensitive to mosquito bites (4, 5). The aim of this study was to examine if ebastine, another non-sedative anti-H1-antihistamine (6, 7), is effective against experimentally produced mosquito bite reactions.

MATERIAL AND METHODS

Subjects

Thirty subjects, 26 females, 4 males (mean age 37 years, range 24–57 years), from the personnel of the University Hospital for Skin and Allergic Diseases, volunteered in the study. All subjects were sensitive to mosquito bites and had had a previously documented mosquito bite reaction, the diameter of which was at least 5 mm at 15 min and/or at 24 h. In addition, all subjects had a positive (over 3 mm diameter) prick test reaction to histamine hydrochloride (10 mg/ml). The mean total IgE level was 146.1 kU/l (range 4–686 kU/l). Thirteen subjects had increased total IgE levels (>130 kU/l), suggesting that they were atopics. The study was performed in February-May 1996, i.e. before the mosquito season. The study was approved by the ethical committee of the hospital and an informed consent was obtained before the study.

Ebastine dosage and observation of side-effects

The study was a double-blind, cross-over study with either 10 mg or 20 mg of ebastine and placebo. Ebastine was in 10 mg tablets and placebo tablets were identical. The drugs were given at 8 a.m. in two 4-day treatment periods. Between these periods was a 3-day wash-out period. The subjects visited the investigators on day 3 and 4 in each treatment period and were asked for any adverse event since the previous visit.

Mosquito exposure and measurement of bite reactions

The mosquito bite exposure was performed between 11 a.m. and 2 p.m. on day 3 of the two treatment periods. The *Aedes aegypti* mosquitoes were from the Institute of Tropical Medicine and Hygiene, Antwerpen, Belgium. One mosquito was put in a small cage, which was placed on the right and left forearm. After feeding, the bite sites were marked. The size of the bite reaction (mm^2) was calculated by measuring two perpendicular diameters in millimeters. Pruritus was evaluated with a visual analogue score (VAS), as previously described (4). The measurements were performed at 15 min and 24 h by the investigators and at 2 and 6 h by the volunteers.

Statistical analysis

The sizes of the bite lesions and pruritus scores from the right and left arms were compiled. The data was then analysed between ebastine and placebo treatment with Wilcoxon signed rank test at every time point, i.e. at 15 min and at 2, 6 and 24 h. In addition, the sum of these four measurements was also analysed. The Mann–Whitney test was used to compare the effects of 10 mg and 20 mg of ebastine.

RESULTS

Completion of the study

Two of the 30 subjects, both of whom completed the trial, were excluded from the analysis becasue of failure to comply with the inclusion criteria. Two subjects withdrew from the study in the second trial period due to possible adverse events. Therefore, 25 subjects remained evaluable in the statistical analysis. Thirteen subjects received 20 mg and 12 were given 10 mg of ebastine. Side-effects could be analysed from 29 subjects during ebastine and from 27 subjects during placebo treatment.

Effect of ebastine on mosquito bite lesions

Size of the bite lesion. Ebastine decreased significantly ($p = 00017$) the size of the bite lesion at 15 min when the effects of 10 mg and 20 mg doses were combined and compared to placebo (Table I). The median size of the bite lesion decreased by 37%, from 44 mm^2 to 27.5 mm^2. At 6 and 24 h the median size of the bite lesions was similar during ebastine and placebo treatments. When the measurements at all four time points were compiled, the median size of the bite lesion was significantly ($p = 00058$) decreased by ebastine treatment (Table I).

Pruritus. Ebastine had a significant ($p < 0.0001$) effect on pruritus at 15 min and the median VAS decreased by 79%, from 7 to 1.5 (ranges 0–9 and 0–6, respectively). At 2, 6, and 24 h VAS scores were low and no significant effect was found.

 ISSN 0001-5555

Table I. *Effect of ebastine on the size of the mosquito bite lesions in 25 mosquito bite-sensitive subjects*

	Size of the bite lesion (mm^2)				
	Ebastine		Placebo		
	Median	Range	Median	Range	P-value*
15 min	27.5	(10–15)	44	(15–95)	0.0017
2 hours	13.5	(0–189)	24	(0–174)	0.064
6 hours	4	(0–157)	4	(0–408)	0.43
24 hours	4	(0–43)	5	(0–353)	0.10
All time points	54.5	(18–252)	90	(22–1024)	0.0058

*Wilcoxon signed rank test.

When the measurements at all four time points were compiled, the median VAS descreased significantly ($p<0.0001$), from 7 to 2 (ranges 0–14.5 and 0–7.5, respectively).

Comparison of 10 mg and 20 mg doses of ebastine

No statistical difference was found when the effects of 10 mg and 20 mg of ebastine were compared at the four time points. When the effects of 10 mg and 20 mg doses were compared separately to placebo, both dosages decreased significantly ($p=0.033$ and 0.028) the size of the bite lesions and also pruritus ($p=0.001$ and 0.0005) at 15 min. When the measurements at four time points were compiled, the effects of 10 mg and 20 mg doses on the size of the bite lesions were almost significant ($p=0.059$ and 0.055) and the effects on the pruritus were significant ($p=0.0005$ and 0.001).

Side-effects

Sedation occurred during ebastine treatment in 6 (21%) and during placebo treatment in 2 (7%) subjects. Due to this 3 subjects withdrew from the study; two of them had received ebastine (20 mg and 10 mg) for 3 days and one subject placebo for 2 days. One subject, who was found to have intolerance to lactose, experienced moderate to severe meteorism during both treatment periods.

DISCUSSION

This placebo-controlled, cross-over study in 25 mosquito bite-sensitive subjects showed that prophylactically given ebastine decreased significantly the size of the 15 min mosquito bite reaction and also had a profound effect on the accompanying pruritus. The fact that ebastine, an effective H1-blocking antihistamine, decreased mosquito bite wealing and accompanying pruritus is not an unexpected finding, since the immediate mosquito bite reaction is mediated by saliva-specific IgE and histamine (2, 3).

The present results, showing that ebastine 10 mg or 20 mg decreases significantly 15-min mosquito bite symptoms, are in good agreement with those reported previously with cetirizine 10 mg (4, 5). Cetirizine also decreased delayed, 12- and 24-h bite symptoms, which seem to be mediated by eosinophils and lymphocytes (5, 8). In agreement with this, cetirizine has been reported to inhibit eosinophil migration and decrease their vacuolization in cutaneous late-phase reactions (9, 10). The obvious reasons for the different results between cetirizine and ebastine seem, however, to be the inclusion criteria and the mosquito species used in the exposures. In the cetirizine study, the subjects were abnormally sensitive to mosquito bites and under placebo most of them showed very large delayed bite reactions, the mean diameter of which was 13 mm at 24 h. In the present study, the corresponding diameter was much smaller, i.e. 2.8 mm, and 15 subjects showed very small or no delayed bite reactions. The reason for this could be that the subjects were exposed to *Aedes aegypti* laboratory mosquitoes and not to *Aedes communis* mosquitoes in the field, as was the case in the cetirizine study. It seems evident, therefore, that a greater number of subjects with intense delayed reactions to mosquito bites should be examined before it can be concluded that ebastine is not effective in the case of delayed mosquito bite reactions.

Newer antihistamines, such as ebastine, may cause sedation in clinical use (7 for ref). In agreement with this, four subjects complained of mild to severe sedation when receiving 20 mg, and 2 subjects when receiving 10 mg ebastine compared to 2 subjects on placebo treatment. Since ebastine 10 mg and 20 mg had similar effects on the mosquito bite symptoms, the 10-mg dose can be recommended for the treatment in order to minimize the possible risk for sedation and other side-effects. The elimination of ebastine may be impaired by erythromycine and ketoconazole, but no effect on the cardiac QTc interval has been documented in man (7).

ACKNOWLEDGEMENTS

We thank the doctors, nurses, and the research and other personnel for volunteering and helping in the study. The study was supported by Rhone-Poulenc-Rorer, Finland.

REFERENCES

1. Reunala T, Brummer-Korvenkontio H, Palosuo T. Are we really allergic to mosquito bites? Ann Med 1994; 26: 301–306.
2. Brummer-Korvenkontio H, Lappalainen P, Reunala T, Palosuo T. Detection of mosquito saliva-specific IgE and IgG antibodies by immunoblotting. J Allergy Clin Immunol 1994; 93: 551–555.
3. Horsmanheimo L, Harvima IT, Harvima RJ, Brummer-Korvenkontio H, François G, Reunala T. Histamine and leukotriene C4 release in cutaneous mosquito-bite reactions. J Allergy Clin Immunol 1996, 98; 408–411.
4. Reunala T, Lappalainen P, Brummer-Korvenkontio H, Coulie P, Palosuo T. Cutaneous reactivity to mosquito bites: effect of cetirizine and development of anti-mosquito antibodies. Clin Exp Allergy 1991; 21: 617–622.
5. Reunala T, Brummer-Korvenkontio H, Karppinen A, Coulie P, Palosuo T. Treatment of mosquito bites with cetirizine. Clin Exp Allergy 1993; 23: 72–75.
6. Mattila MJ, Aranko K, Kuitunen T. Diazepam effects on the performance of healthy subjects are not enhanced by the treatment with the antihistamine ebastine. Br J Clin Pharmacol 1993; 35: 272–277.
7. Wiseman LR, Faulds D. Ebastine: a review of its pharmacological properties and clinical efficacy in the treatment of allergic disorders. Drugs 1996; 51: 260–277.
8. Karppinen A, Rantala I, Vaalasti A, Palosuo T, Reunala T. Effect of cetirizine on the inflammatory cells in mosquito bites. Clin Exp Allergy 1996; 26: 703–709.
9. Fadel R, Herpin-Richard N, Rihoux J-P, Henoqo E. Inhibitory effect of cetirizine 2HCl on eosinophil migration in vivo. Clin Allergy 1987; 17: 373–379.
10. Snyman JR, Sommers DK, Gregorowski MD, Boraine H. Effect of cetirizine, ketotifen and chlorpheniramine on the dynamics of the cutaneous hypersensitivity reaction: a comparative study. Eur J Clin Pharmacol 1992; 42: 358–362.