SHORT REPORT

Rupatadine 10 mg in the treatment of immediate mosquito-bite allergy

A. Karppinen,[†] H. Brummer-Korvenkontio,[‡] T. Reunala,[†] I. Izquierdo[§,*]

[†]Department of Dermatology, Tampere University and University Hospital, Tampere, Finland
[‡]National Institute for Health and Welfare, Helsinki, Finland
[§]Clinical Development Unit, Medical Area, J. Uriach y Compañia, S.A. Barcelona, Spain
*Correspondence: I. Izquierdo. E-mail: clin-izquierdo@uriach.com

Abstract

Background People frequently experience wealing and delayed papules from mosquito bites. Wealing is mediated by antisaliva IgE antibodies and histamine.

Rupatadine is a new antihistamine effective in allergic rhinitis and urticaria, but the effect on mosquito-bite allergy is not known.

Objective To determine the effectiveness of rupatadine in inmediate mosquito-bite allergy-confirmed adult patients.

Methods A double-blind, placebo-controlled, cross-over study was performed with rupatadine 10 mg and matched placebo in 30 mosquito-bite-sensitive adults. The mean age was 37 years and the subjects had suffered from harmful mosquito bites for a mean of 15 years. Either rupatadine or placebo was taken at 08:00 AM for 4 days, followed by a 5 day wash out period and then alternative treatment was given for 4 days. On day 3, in both drug periods the subjects received two *Aedes aegypti* mosquito-bites on the forearm. The size of lesions and intensity of pruritus [visual analogue scale (VAS)] were measured after 15 min bite reaction.

Results Twenty-six subjects were analysed for efficacy. The size of the 15 min bite reaction under placebo was of 106 mm^2 and under rupatadine, of 55 mm^2. This is a significant decrease (48%; $P = 0.0003$). The accompanying pruritus decreased from 60 (VAS; median) under placebo to 47.5 under rupatadine, which also is a significant ($P = 0.019$) difference. There was no significant ($P = 0.263$) difference in adverse events under rupatadine and placebo.

Conclusion The present placebo-controlled study in mosquito-bite-sensitive adults shows that rupatadine 10 mg prophylactically given is an effective treatment for the mosquito-bite wealing and skin pruritus.

Received: 19 December 2011; Accepted: 9 March 2012

Conflicts of interest

Dr Izquierdo is an employee from Medical Area of J Uriach and Cia, S.A. There were no conflicts of interest with the rest of authors.

Introduction

Mosquitoes frequently cause harmful bite reactions such as immediate weals and delayed bite papules in children and adults. People exposed for the first time to the bites of certain mosquito species are first non-reactive, but after repeated bites, they become sensitized and bite reactivity often persists for years.[1] In heavily exposed areas such as Nordic countries in Europe, Canada and Japan, children and most adults are sensitized and react to the bites of *Aedes* mosquitoes.[2–5] The most common bite reactions are immediate weals and pruritic bite papules, which may last several days.[6] Systemic reactions to the bites may also occur.[7]

Mosquito-bite wealing is known to be mediated by antisaliva IgE antibodies and histamine.[8] In agreement with this, oral second generation antihistamines, cetirizine and ebastine in adults and loratadine in children, have been shown to decrease wealing and accompanying pruritus in placebo-controlled trials.[9–11]

Rupatadine is a potent second generation, selective long-acting histamine H1 receptor[12] with a dual activity through its interaction with specific platelet-activating factor (PAF) receptors.[13] Rupatadine showed a dose-related suppression of the weal and flare produced in response to intradermally injected histamine or PAF. Onset of antihistamine action appeared 1 to 2 h after oral rupatadine fumarate administration, whereas the inhibition of the PAF-induced platelet aggregation appeared 2 to 6 h after administration.[14]

The purpose of the study was to evaluate the effectiveness of prophylactically administered rupatadine 10 mg against immediate and delayed symptoms caused by mosquito bites.

© 2012 The Authors

Methods

Study design and treatments assessed

The study design was a randomized, double-blind, placebo-controlled, cross-over study with either 10 mg rupatadine or placebo on 30 mosquito-bite allergic adult subjects (Fig. 1).

The subjects received four tablets of the randomized drugs at the beginning of each of the two trial periods and they took the drugs at 08:00 AM. All subjects were given at the onset of the study 1% hydrocortisone cream to be used as rescue medicine for possible intense itching. The investigator had ensured that the subjects clearly understood and agreed to comply with given instructions. The study was approved by Ethics Committees of the Tampere University Hospital, and written informed consent was obtained from all subjects.

Inclusion and exclusion criteria

Volunteers aged between 18 and 65 years, with history of suffering from mosquito-bite reactions and showing at inclusion at least 5-mm diameter weal (at 15 min) from *Aedes aegypti* mosquito bite, were included in the study.

Subjects with anaphylaxis from mosquito bites or with negative cutaneous reaction test were not included. Assessed at screening, prior to randomization, treatments with oral antihistamine, corticosteroid or non-steroid anti-inflammatory drug (NSAID) use within 2 weeks prior to inclusion, were also considered as exclusion criteria.

Mosquitoes and measurement of the bites lesions

The measurements were selected based on published literature, according to validated experimental model widely used by other antihistamines in this condition.[9–11] *A. aegypti* mosquito eggs were obtained from a strain reared in the Laboratoire de Lutte contre le Insectes Nuisibles, Montpellier, France. The mosquito strain is free from any viral or other pathogens. Eggs collected on moist paper were air dried and then transported to doctor Henrikki Brummer–Korventio, National Institute of Public Health, Helsinki, Finland. They were hatched to larvae and then reared to adult mosquitoes. These were collected and then transported to the study site in Tampere.

In both drug periods, two mosquitoes in a cage were allowed to feed on the forearm of the subjects on day 3, between noon and 03:00 PM (see Fig. 2). The bite reaction was measured in two perpendicular diameters at 15 min and 24-h time. The size of the bite was then expressed as mm^2. Pruritus was evaluated using a 100-mm visual analogue scale (VAS) ranging from 0 (no pruritus) to 100 (very intense pruritus).

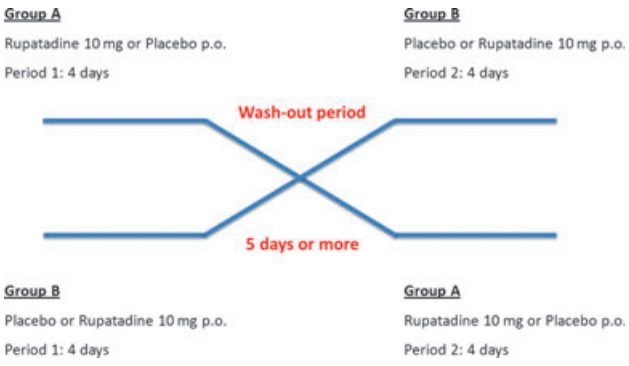

Figure 1 New cross-over study design.

Statistical analysis

Wilcoxon's signed rank test with Hommel's adjusted *P*-value was used to analyse the bite lesion size in mm^2 (sum of the two bite lesions) and accompanying pruritus (VAS) measured under rupatadine and under placebo. Calculations were performed separately for the measurements at 15 min and at 24 h. P value < 0.05 was considered significant.

Results

Disposition of study subjects

Thirty Caucasian subjects were randomized and completed the study. There were 26 women and 4 men. Their mean age was

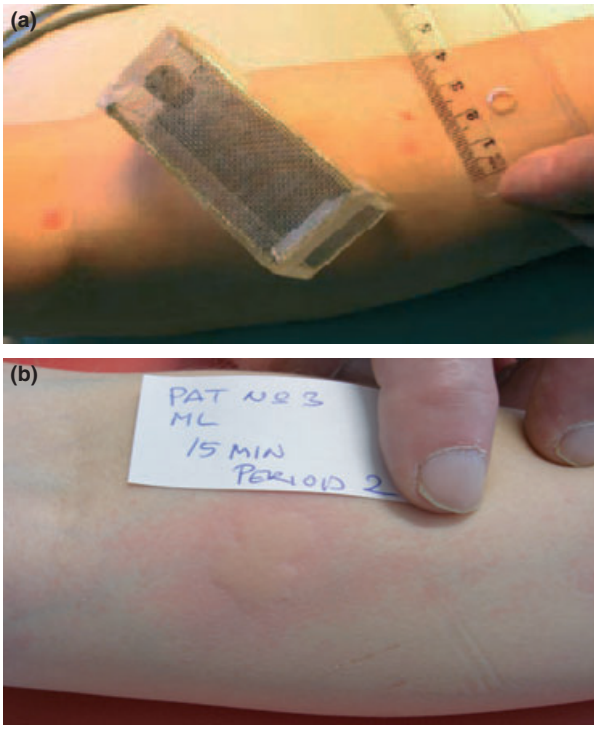

Figure 2 The bite exposure was performed with two *Aedes aegypti* laboratory mosquitoes in a cage (a). The size of bite weals was measured at 15 min and 24 h, as described in the text (b).

© 2012 The Authors
Journal of the European Academy of Dermatology and Venereology © 2012 European Academy of Dermatology and Venereology

37 years (range: 20–61 years) and their weight of 66 kg (range: 56–91 kg). The mean length of history of mosquito-bite allergy was 16 years (range: 5–40 years).

All 30 volunteers were evaluated for safety of whom 26 volunteers were available for efficacy evaluation. Four subjects were excluded from the main efficacy population. One subject did not have all efficacy evaluations in both drug periods available and was excluded. Two subjects had at 15 min in both drug periods, bite lesions which were smaller than 25 mm^2 and were also excluded. Another subject showed at 15 min a bite lesion, which was 50% smaller than the baseline measurement. Due to this large deviation, it was excluded from the efficacy analysis.

There was a clear statistically significant ($P < 0.001$) reduction in bite lesion size and the accompanying pruritus ($P < 0.05$) at 15 min with rupatadine 10 mg compared with placebo (Fig. 3). The median weal size was reduced by 48% from 106 mm^2 in the placebo to 55 mm^2 in rupatadine group. The mean size of the 24-h delayed bite lesion also decreased by 54% from 23 mm^2 in the placebo group to 10.5 mm^2 in rupatadine, but this difference was not significant. Rupatadine decreased significantly ($P < 0.05$) the accompanying pruritus at 15 min by 21%, and the median VAS scores were 60 mm^2 in the placebo group and 47.5 mm^2 in the rupatadine group (Fig. 3). The pruritus at 24 h disappeared in both treatment groups.

To assess the effect of rupatadine 10 mg only on those patients who were reactive to the bites at 24 h, a subset analysis was performed, excluding the following non-reactive subjects: (i) All subjects ($n = 10$) in whom the size of the bite lesion under placebo was 1 mm^2 or zero; and (ii) all subjects ($n = 20$) in whom VAS under placebo was zero. In the 20 subjects with delayed bite lesions, rupatadine decreased the size of the 24 h bite lesions (13.5 mm^2 vs. 33 mm^2) by 60%, but was not statistically significant ($P = 0.07$). Accompanying pruritus in the 10 subjects available was also reduced by 23%, but this effect was not statistically significant probably due to the low number of cases.

There was no significant difference in adverse events between the two treatments (four cases in placebo; eight cases in Rupatadine group). Eight volunteers reported sedation in nine cases (8 = rupatadine, 1 = placebo). No serious adverse events were reported during the study.

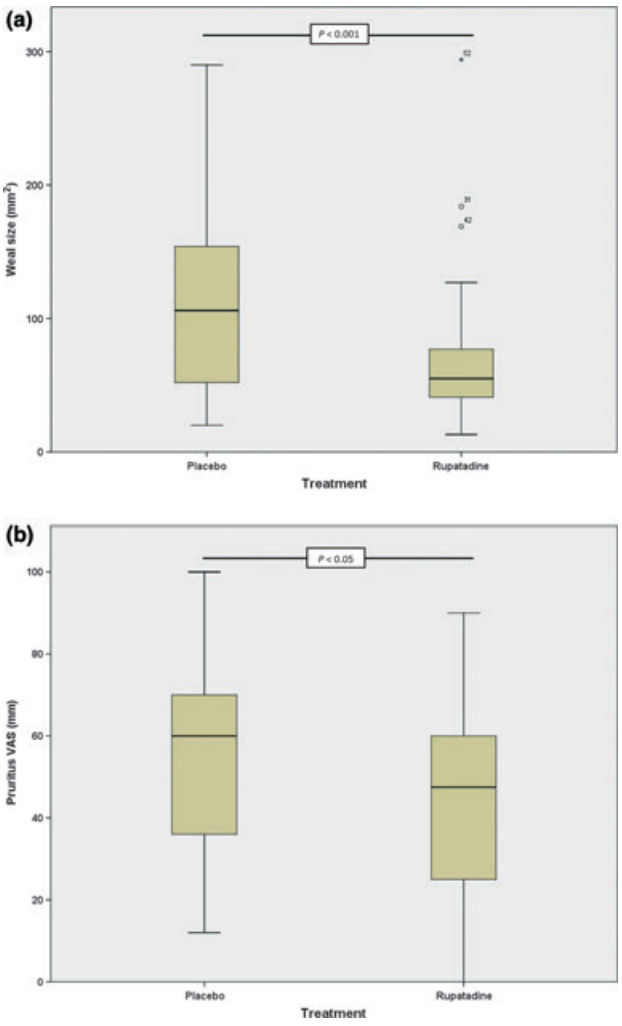

Figure 3 Weal size (a) and accompanying pruritus (b) in 26 mosquito-bite-sensitive subjects treated with rupatadine 10 mg and placebo. Data are expressed in median and 25–75 percentiles (Box-plots) and error bar. The points on frame represent the outlier cases.

Discussion

The present placebo-controlled, cross-over study in 26 mosquito bite sensitive subjects showed that prophylactically administered rupatadine 10 mg decreased the size of immediate mosquito-bite lesions, i.e. weals at 15 min, by a total of 48% when compared with placebo. This treatment effect was statistically significant. Rupatadine 10 mg also significantly decreased accompanying pruritus of 15 min-long bite lesions. These results are in agreement with the previous studies performed in a similar setting with cetirizine 10 mg and ebastine 10 mg,[9,10] with decreased wealing by 30–40%, or with loratadine 10 mg in children[15] with a reduction of 45%, and recently with levocetirizine 5 mg with decrease in the weal size by 60%.[11] The effect of these second generation antihistamines is not unexpected, as wealing reaction from mosquito bites is a Type I allergic reaction mediated by IgE anti-saliva antibodies and finally, histamine is released into the skin during wealing.[7,8]

The effect of rupatadine on the size of 24-h bite lesions could be analysed in 20 subjects and the accompanying pruritus in only 10 subjects. An improvement trend with rupatadine could be seen on these delayed bite symptoms, although a significant level was not reached. A reasonable explanation for these findings is that some subjects did not show a large

© 2012 The Authors

delayed bite reactions, and it seems evident therefore that a greater number of subjects with intense delayed reactions to mosquito bites should be examined at screening phase before it can be concluded that rupatadine is not effective in the case of delayed mosquito bite reactions.

In the present study, sedation was reported more often under rupatadine 10 mg than under placebo, but the difference was not statistically significant. A similar trend in sedation was also reported in the previous studies.[7–10] However, sedation was not a significant problem in the treatment of mosquito-bite reactions because no drop-outs occurred in the present study or in our previous studies.[7,8] In fact, when the subjects may notice that an antihistamine really alleviates their symptoms, they will obviously tolerate the sedation as long as it remains mild.

In conclusion, the present double-blind, placebo-controlled study performed in 30 mosquito-bite allergic subjects with *A. aegypti* laboratory mosquitoes showed that prophylactically administered rupatadine 10 mg has a significant decreasing effect on the size of immediate bite lesions and intensity of the accompanying pruritus.

Acknowledgements

We thank the study nurse Anna-Liisa Talvitie, Josep Giralt for helping with new statistical box-plot analysis and all volunteers for participating in the study. This study was supported by J Uriach and Cia, S.A., Spain.

References

1 Reunala T, Brummer-Korvenkontio H, Palosuo T. Are we really allergic to mosquito bites? *Ann Med* 1994; **26**: 301–306.
2 Konishi E. Distribution of immunoglobulin G and E antibody levels to salivary gland extracts of *Aedes albopictus* (Diptera: Culicidae) in several age groups of a Japanese population. *J Med Entomol* 1990; **27**: 519–522.
3 Peng Z, Simons FE. Cross-reactivity of skin and serum specific IgE responses and allergen analysis for three mosquito species with worldwide distribution. *J Allergy Clin Immunol* 1997; **100**: 192–198.
4 Brummer-Korvenkontio H, Palosuo K, Palosuo T, Brummer-Korvenkontio M, Leinikki P, Reunala T. Detection of mosquito saliva-specific IgE antibodies by capture ELISA. *Allergy* 1997; **52**: 342–345.
5 Palosuo K, Brummer-Korvenkontio H, Mikkola J, Sahi T, Reunala T. Seasonal increase in human IgE and IgG4 antisaliva antibodies to *Aedes* mosquito bites. *Int Arch Allergy Immunol* 1997; **114**: 367–372.
6 Reunala T, Brummer-Korvenkontio H, Palosuo K *et al.* Frequent occurrence of IgE and IgG4 antibodies against saliva of *Aedes comunis* and *Aedes aegypti* mosquitoes in children. *Int Arch Allergy Inmunol* 1994; **104**: 366–371.
7 Peng Z, Beckett AN, Engler RJ, Hoffman DR, Ott NL, Simons FER. Immune responses to mosquito saliva in 14 individuals with acute systemic allergic reactions to mosquito bites. *J Allergy Clin Immunol* 2004; **114**: 1189–1194.
8 Horsmanheimo L, Harvima IT, Harvima RJ, Brummer-Korvenkontio H, Francois G, Reunala T. Histamine and leukotriene C4 release in cutaneous mosquito bite reactions. *J Allergy Clin Immunol* 1996; **98**: 408–411.
9 Reunala T, Brummer-Korvenkontio H, Karppinen A, COulie P, Palosuo T. Treatment of mosquitos bites with cetirizine. *Clin Exp Allergy* 1993; **23**: 72–75.
10 Karppinen A, Kautiainen H, Petman L, Burri P, Reunala T. Comparison of cetirizine, ebastine and loratadine in the treatment of immediate mosquito-bite allergy. *Allergy* 2002; **57**: 534–537.
11 Karppinen A, Brummer-Korvenkontio H, Petman L, Kautiainen H, Hervé JP, Reunala T. Levocetirizine for treatment of immediate and delayed mosquito bite reactions. *Acta Derm Venereol* 2006; **86**: 329–331.
12 Mullol J, Bousquet J, Bachert C *et al.* Rupatadine in allergic rhinitis and chronic urticaria. *Allergy* 2008; **63**(Suppl. 87): 5–28.
13 Merlos M, Giral M, Balsa D *et al.* Rupatadine, anew potent, orally active dual antagonist of histamine and platelet -activating factor (PAF). *J Pharmacol Exp Ther* 1997; **280**: 114–121.
14 Church MK. Efficacy and tolerability of rupatadine at four times the recommended dose against histamine and PAF induced flare responses and *ex vivo* platelet aggregation in healthy males. *Br J Dermatol* 2010; **163**: 1330–1332.
15 Karppinen A, Kautiainen H, Reunala T, Petman L, Reunala T, Brummer-Korvenkontio H. Loratadine in the treatment of mosquito-bite-sensitive children. *Allergy* 2000; **55**: 668–671.

© 2012 The Authors
Journal of the European Academy of Dermatology and Venereology © 2012 European Academy of Dermatology and Venereology