

ORIGINAL ARTICLE

Comparison of the efficacy of fexofenadine 120 and 240 mg/day on chronic idiopathic urticaria and histamine-induced skin responses in Japanese populations

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Background: H1-antihistamines are the first-line treatment of chronic idiopathic urticaria (CIU), but CIU is occasionally refractory to the conventional treatment doses. Guidelines in Europe recommend increasing doses as second-line therapy; however, more supportive evidences for these guidelines are required to justify this management strategy. **Methods:** In this study, the authors evaluated the effect of conventional and double doses of fexofenadine HCl on CIU and on histamine-induced skin responses by iontophoresis using visual and laser Doppler imaging scales in healthy donors. **Results:** Cutaneous manifestations in CIU and histamine-induced flare and itch in healthy donors were attenuated more extensively by a double dose of fexofenadine HCl compared with a conventional dose. **Conclusion:** The above findings support the management strategy that increasing the dose of non-sedative antihistamines is the second-line treatment choice for refractory CIU even in Japanese populations.

Key words: fexofenadine HCl, histamine, chronic idiopathic urticaria

Introduction

Chronic idiopathic urticaria (CIU) is defined by daily symptoms including itching, hives and/or edema that recur for more than 6 weeks without identifiable causes (1). CIU is anxiety provoking and impacts individuals' quality of life to the same extent as severe coronary artery disease or respiratory allergies (2,3).

Histamine is released from skin mast cells to produce flare and wheal with pruritus by acting on blood vessels and sensory nerves (1,4). Histamine modulates inflammatory conditions by acting on keratinocytes and other cells (5–9). The guidelines recommend that the first line of treatment for urticaria should be with non-sedating H1-antihistamines (1). However, studies of patients with CIU revealed that some patients exhibited a limited response to treatment with conventional doses of antihistamines (10).

The second line of treatment for CIU is to increase the antihistamine dosage in patients not responding to conventional posology before considering alternative treatment strategies according to the guidelines in Europe (1). In addition, a recent study has demonstrated that increasing the doses of the antihistamines levocetirizine and desloratadine improved the quality of life of patients with refractory CIU in Europe (11). In the meantime, it has also been reported that increasing the dose of the

most widely used antihistamine, fexofenadine HCl, from 60 to 240 mg twice daily did not improve urticaria exhibiting moderate to severe symptoms in the USA (12).

To provide further evidence for the rationale of increasing the dose of fexofenadine HCl for CIU, the authors performed a pilot study to assess the efficacy of using up to two times the conventionally prescribed doses of the second-generation antihistamine, fexofenadine HCl in patients with CIU. In addition, they evaluated histamine-induced cutaneous reactions using iontophoresis in healthy donors.

Materials and methods

Visual analog scale and severity index

The authors evaluated the severity of pruritus by visual analog scale (VAS) score (100% VAS score) (13) and severity index from 12 h preceding the visit to their hospital. The symptoms of urticarial lesions and pruritus were determined by the severity index (i.e. 0, none; 1, mild; 2, moderate; 3, intense; 4, severe; 5, shock) in accordance with the Japanese Dermatological Association guidelines 2005 on the classification of urticaria (14).

Patients

Twenty Japanese patients (12 males and 8 females; age 36.2 ± 6.6 years) with CIU refractory to conventional doses of second-generation antihistamines were enrolled. Patients who had suffered from urticarial wheals for at least six consecutive weeks before entry were enrolled in this study. Patients with urticaria associated with an underlying disease or physical urticaria due to cold, heat or sun were excluded. Informed consent was obtained from all patients.

Histamine-induced cutaneous reactions by iontophoresis

A randomized, double-blinded, placebo-controlled, cross-over trial was performed on eight healthy Japanese volunteers (two males and six females; age 30.5 ± 4.9 years) with no history of allergy. None of the participants had received any oral or topical medication for at least 1 week prior to the experiment. The local ethics committee approved this study, and informed written consent was obtained from all participants.

Histamine dihydrochloride (Wako Pure Chemical Industries Ltd., Tokyo, Japan; 1 mg/ml) was administered to the skin at the antecubital fossa using an iontophoreser (Nihon-Koden Ltd., Tokyo, Japan). The flare and wheal responses were assessed

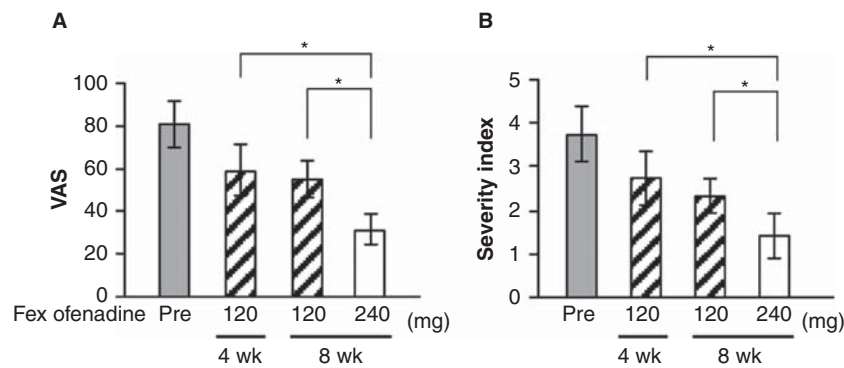


Figure 1. VAS scores and severity index in CIU after treatment with fexofenadine HCl. (A, B) The VAS scores (A) and severity index (B) in patients with CIU before (pre) and after treatment are shown. The patients were prescribed 60 mg fexofenadine twice a day (120 mg/day) for 4 weeks ($n = 20$), followed by 60 or 120 mg fexofenadine twice a day (120 and 240 mg/day, respectively) for another 4 weeks ($n = 10$, each group). * $p < 0.05$ between the indicated groups by Tukey's non-parametric multiple comparison test.

5 min after the end of iontophoresis, and administration of placebo or fexofenadine HCl (Allegra, Sanofi-Aventis Pharma, Frankfurt, Germany) was then carried out. The maximum (r_1) and orthogonal diameters (r_2) were visually measured and the flare and wheal areas were calculated as $r_1/2 \times r_2/2 \times 3.14$. In addition, changes in skin blood flow were assessed by scanning

laser Doppler imaging (LDI) 2 (Moor Instruments Ltd., Axminster, UK), and flare areas were calculated from the calibrated images (15).

The participants were asked to report the intensity of the evoked sensation on a numerical scale of 0 (no sensation) to 10 (the maximum sensation imaginable) at 10-s intervals for

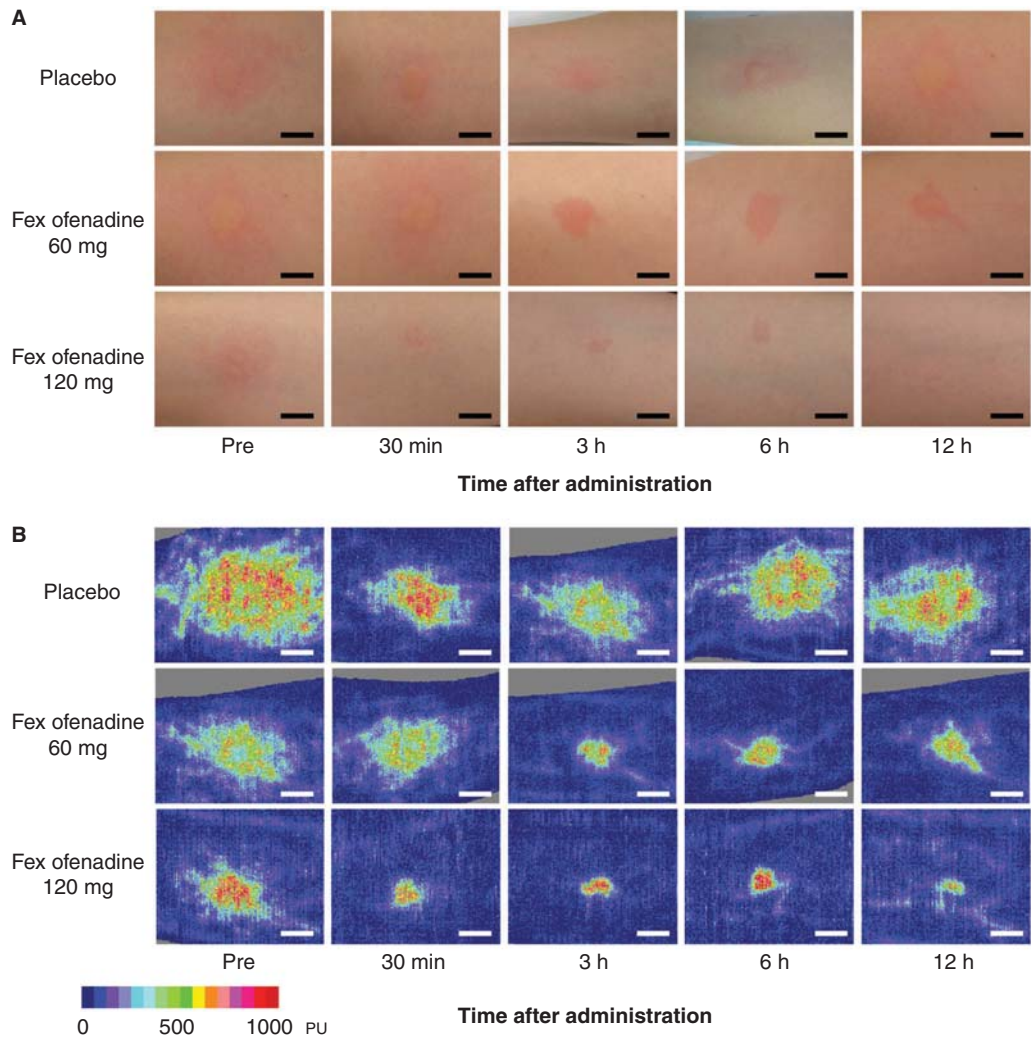


Figure 2. Clinical images of histamine-induced flares and wheal. (A) Clinical appearances. Representative clinical photos of histamine-induced flare and wheal at indicated time points after placebo and 60 and 120 mg fexofenadine. Bars: 5 mm. (B) LDI. Scanning LDI taken at indicated time points. PU: scanning laser Doppler perfusion units. Bars: 5 mm.

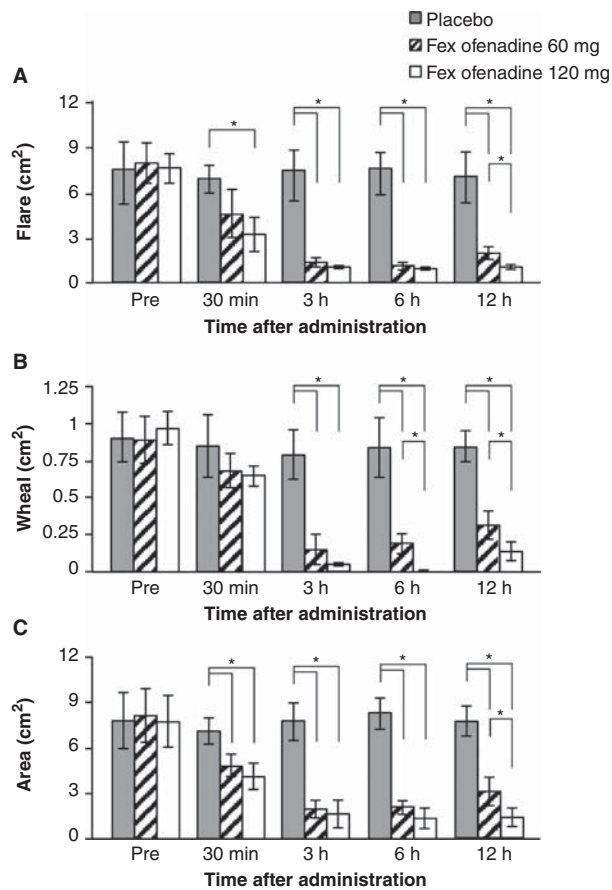


Figure 3. Evaluation of antihistamines on histamine-induced flare and wheal responses. (A) The flare size induced by histamine before and after administration. (B) The size of wheal induced by histamine before and after administration. (C) The area of flares evaluated by LDI. Placebo and 60 and 120 mg fexofenadine are shown ($n = 8$ for all treatments). Results are presented as mean $\pm$ SD. * $p < 0.05$ between the indicated groups by Tukey's non-parametric multiple comparison test.

10 min after the iontophoresis. The area under curve (AUC) of the ratings for 10 min (min 0, max 610) was calculated for analysis.

Statistical analyses

All data were analyzed using Tukey's non-parametric multiple comparison test.

Results

The patients with CIU received conventional dose (60 mg) of fexofenadine HCl twice a day, which is a regular dose in Japan, for 4 weeks. The authors evaluated the severity of pruritus by the VAS score and the severity index. The effects of 60 mg fexofenadine HCl twice a day on pruritus and the severity index in refractory CIU were limited (Figure 1A and B). Next, the patients were prescribed 60 or 120 mg fexofenadine HCl randomly twice a day for another 4 weeks. The authors evaluated pruritus and the severity index from 12 h preceding the visit, and demonstrated that the 100% VAS score of pruritus and the severity index were significantly decreased by treatment with 120 mg fexofenadine HCl twice a day compared with that with 60 mg fexofenadine HCl twice a day (Figure 1A and B). None of the patients complained of fatigue and/or sleepiness on increasing the dosage.

Next, the authors evaluated the wheal and flare responses to histamine. Histamine iontophoresis induced wheal and flare,

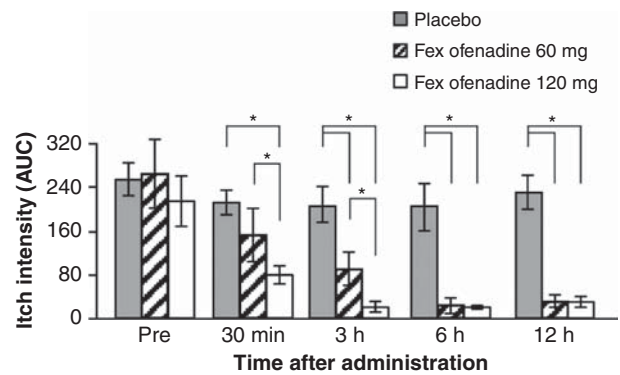


Figure 4. The AUC of itch sensation induced by histamine iontophoresis. The AUC of itch intensity. Placebo and 60 and 120 mg fexofenadine are shown ($n = 8$). * $p < 0.05$ between the indicated groups by Tukey's non-parametric multiple comparison test.

which persisted for at least 12 h in all healthy volunteers (Figures 2 and 3). The sizes of histamine-induced flare were comparable among placebo-, 60 mg of fexofenadine HCl- and 120 mg of fexofenadine HCl-treated groups before antihistamine administration (Figures 2A and 3A). Both doses of fexofenadine HCl significantly suppressed flare areas compared with placebo treatment at 3, 6 and 12 h after treatment (Figures 2A and 3A). However, at 30 min after administration, 120 mg fexofenadine HCl treatment significantly suppressed the flare size, but 60 mg fexofenadine HCl did not (Figure 3A). Consistent with the finding of the flare formation measured visually (Figure 3A), similar results were obtained when the flare sizes were evaluated using LDI (Figure 3C).

By contrast, both doses of fexofenadine HCl suppressed the wheal response at 3, 6 and 12 h, but not at 30 min after treatment (Figure 3B). In addition, wheal development at 6 and 12 h after administration was more pronouncedly suppressed by 120 mg fexofenadine HCl treatment than by 60 mg fexofenadine HCl treatment (Figure 3B).

The author also evaluated the effect of antihistamines on itch intensity. Histamine-induced pruritus was suppressed by both doses of fexofenadine HCl at 3, 6 and 12 h after administration. The inhibitory effect of 120 mg fexofenadine HCl treatment was more prominent at 30 min and 3 h after the administration (Figure 4). These findings suggest that a double dose of fexofenadine HCl elicits a rapid and sustained effect on histamine-induced skin inflammatory responses.

Discussion

In this pilot study, the authors have demonstrated that a double dose of fexofenadine HCl treatment strongly suppressed pruritus and the severity index in CIU and suppressed histamine-induced flare and wheal formation and itch in healthy donors at certain time points when compared with a conventional dose of fexofenadine HCl treatment.

Fexofenadine HCl is a non-sedating second-generation antihistamine with short T_{max} values. This drug possesses suppressive functions on pruritus that is accompanied by urticaria. It has been reported that increasing the dose of fexofenadine HCl from 60 to 240 mg twice daily did not increase the control of urticaria with moderate to severe symptoms in the USA (12). In this study, the authors applied increasing doses to CIU in Japanese patients. They found that a double dose stronger suppressed the symptoms of CIU, histamine-induced flare formation, wheal and itch

compared with a single dose. In addition, none of the patients complained of fatigue and/or sleepiness on increasing the dosage. These findings support the rationale for increasing the dosage of a non-sedating antihistamine in patients not responding to the conventional posology recommended by the guidelines in Europe.

Conclusion

The limitations of the study are the small number of enrolled participants, the dosage of the drug (only two doses) and the study design (e.g. this study is not double-blind). In Western countries, fexofenadine is commonly applied 120–180 mg daily, but in Japan dose of 60 mg twice a day is used. In addition, a histamine-induced skin reaction was performed in only healthy donors. It would be of interest to apply this study to patients with CIU. Although study limitations exist, these results suggest that a double dose of fexofenadine treatment suppresses skin symptoms more rapidly, profoundly and sustainably than a conventional dose of fexofenadine treatment. A randomized, double-blind, controlled trial is needed to confirm the clinical relevance of these findings.

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Declaration of interest: The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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