

A Double Dose of Levocetirizine Leads to Better Control of Histamine-Induced Flare, Wheal and Itch in Healthy Donors

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Key Words

Levocetirizine · Histamine · Urticaria · Itch · Flare · Iontophoresis

Abstract

Levocetirizine is classified as a nonsedating second-generation antihistamine. This drug is used to treat allergic disorders such as urticaria and pruritus. Thus far, studies have demonstrated an increase in efficacy for refractory urticaria by increasing doses of antihistamines; however, more lines of supportive evidence for these guidelines are required to justify this management strategy. In this study, we found that a double dose of levocetirizine suppressed histamine-induced flare formation more rapidly and sustainably, and wheal and itch more extensively, compared with the conventional dose using both visual and laser Doppler imaging scales in a noninvasive manner. These results suggest that double-dosed levocetirizine treatment suppresses histamine-induced skin symptoms more rapidly, profoundly and sustainably than conventionally dosed levocetirizine treatment.

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Introduction

Histamine is released from skin mast cells, and it induces flare and wheal with pruritus by acting on blood vessels and sensory nerves (as e.g. in urticaria) [1]. Histamine is also known to modulate inflammatory conditions by acting on keratinocytes and other cells [2]. Oral antihistamines are the first-line treatment for urticaria. Their efficacy, speed, duration of action and side effects, such as drowsiness and sedation, depend upon the properties of each drug [1, 3]. The second-generation antihistamines are generally as effective as and better tolerated (i.e. there are fewer sedative and anticholinergic effects) than the first-generation antihistamines [3]. Increasing doses of second-generation antihistamines up to 4 times the conventional dose are advocated in international guidelines on chronic urticaria (CU), based largely upon expert opinions [1, 3, 4]. Thus far, studies have demonstrated an increase in efficacy for refractory urticaria by increasing doses of antihistamines [5]; however, there are some studies stating that high-dose antihistamine is minimally effective [6]. Therefore, more lines of supportive evidence are required for these guidelines to justify this management strategy. In this study, we evaluated the effect of the

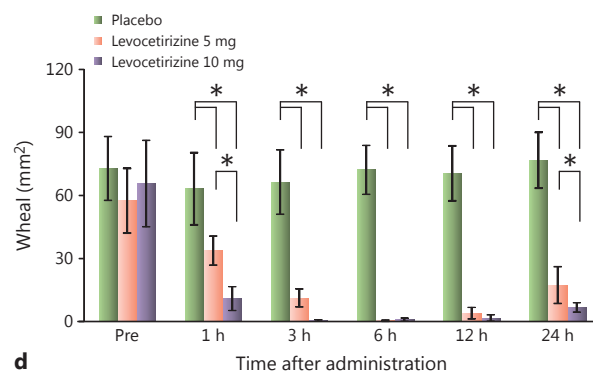
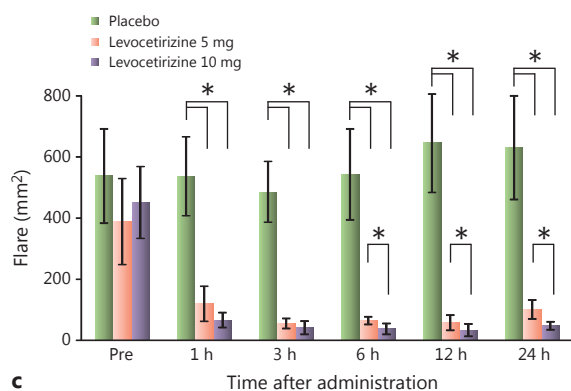
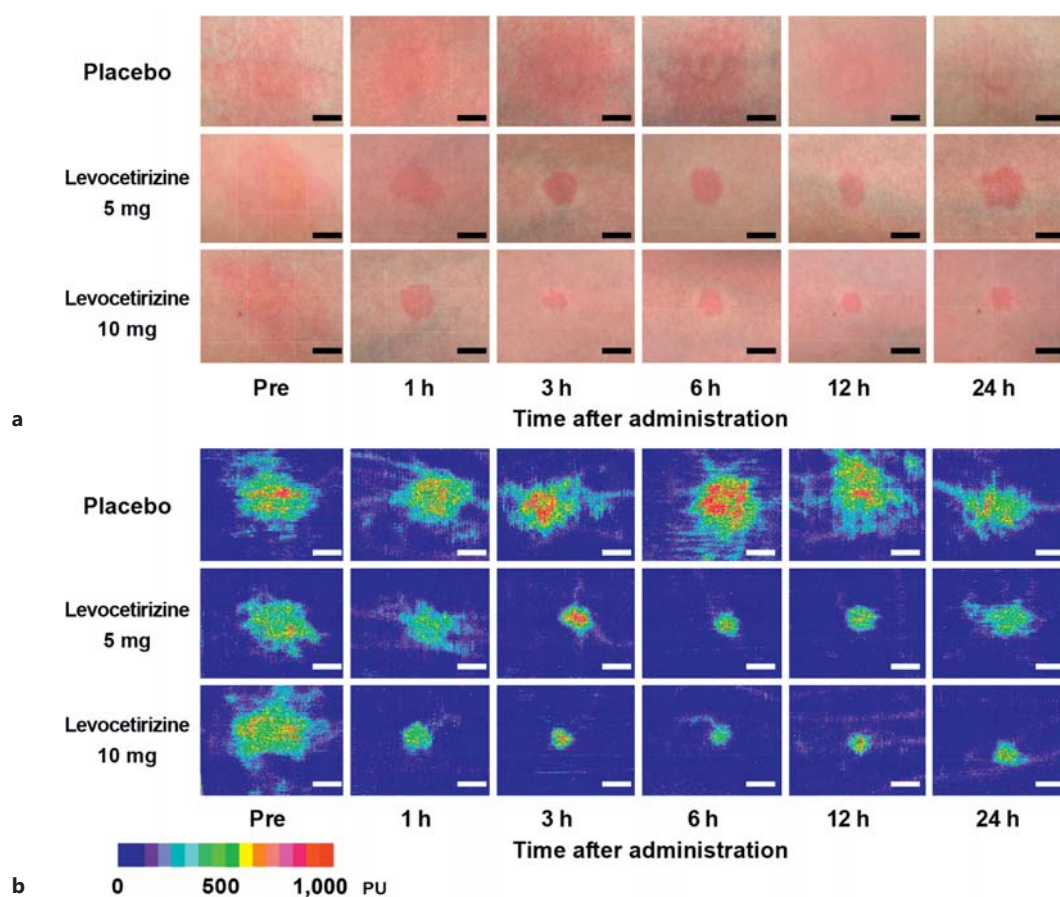


Fig. 1. Clinical images and evaluation of the effect of antihistamines on histamine-induced flare and wheal. Pre = Before administration. **a** Clinical appearances. Representative clinical photographs of histamine-induced flare and wheal at indicated time points after placebo, 5 mg levocetirizine and 10 mg levocetirizine.

Scale bars = 5 mm. **b** LDI scans taken at indicated time points. PU = Perfusion units. Scale bars = 5 mm. **c, d** Flare size (**c**) and the size of wheal (**d**) induced by histamine before and after administration. Results are presented as means $\pm$ SD. * $p < 0.05$ between indicated groups by Tukey's nonparametric multiple comparison test.

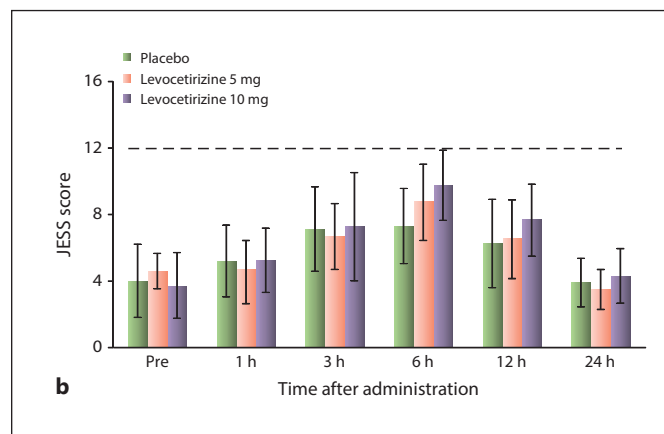
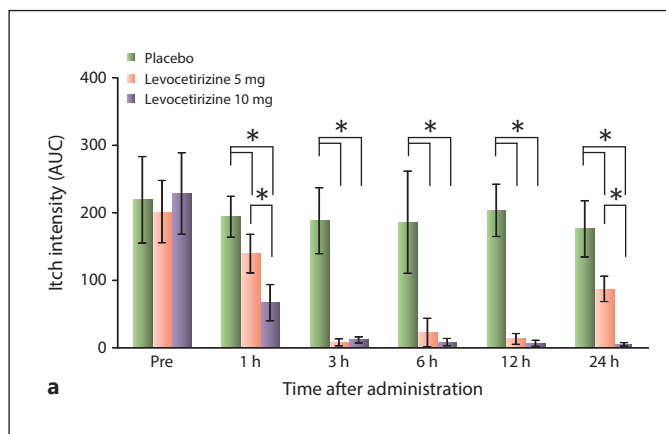


Fig. 2. Evaluation of the effect of antihistamines on histamine-induced itch responses (**a**) and JESS scores (**b**). Placebo, 5 mg levocetirizine and 10 mg levocetirizine are shown ($n = 10$). Results are presented as means $\pm$ SD. * $p < 0.05$ between indicated groups by

Tukey's nonparametric multiple comparison test. AUC = Area under the curve; Pre = before administration. **b** Dotted line: threshold value that can be evaluated as drowsiness.

normal dose (5 mg/day) and double dose (10 mg/day) of levocetirizine on histamine-induced skin responses, using iontophoresis with visual and laser Doppler imaging (LDI) scales in healthy volunteers.

Materials and Methods

This study was performed as a randomized, double-blind, placebo-controlled crossover trial enrolling 10 healthy volunteers (6 men and 4 women; age: 31.0 ± 5.2 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 written informed consent was obtained from all participants. Histamine dihydrochloride (Wako Pure Chemical Industries Ltd., Tokyo, Japan) was dissolved in distilled water at a concentration of 1 mg/ml. The resulting compound was administered to the skin at the antecubital fossa, using an iontophoreser (Nihon-Koden Ltd., Tokyo, Japan) with a 0.5-cm² cotton applicator at a constant current of 0.1 mA for 30 s. The flare and wheal responses were assessed 5 min after the end of iontophoresis, and then placebo or antihistamines were administered at the fixed time point. 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 using a moorLDI2 imager (Moor Instruments Ltd., Axminster, UK), and flare areas were calculated from the calibrated images using the manufacturer's software [7]. Responses to the test stimuli were assessed before and 1, 3, 6, 12 and 24 h after administration of the medication. The normal dose or a double dose of levocetirizine was administered orally to each healthy volunteer in a randomized order. There was a washout period of at least 1 week between each experiment to prevent any carryover effect. Tests were performed at least 2 h after meals. The temperature of the room was maintained at 23°C. 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-second intervals for 10 min after the iontophoresis. The area under the curve of ratings for 10 min (min. 0, max. 610) was calculated for analysis.

Results

Histamine iontophoresis induced wheal and flare in all volunteers (fig. 1), and levocetirizine significantly suppressed flare and wheal areas compared with placebo treatment 1, 3, 6, 12 and 24 h after administration (fig. 1). Levocetirizine (10 mg) significantly suppressed the histamine-induced flare intensity 6, 12 and 24 h (fig. 1c) and wheal intensity 1 and 24 h after administration (fig. 1d) compared with 5 mg of levocetirizine. Histamine-induced wheal was suppressed by both doses of levocetirizine at all time points, but the inhibitory effect was more prominent 1 and 24 h after the administration of 10 mg compared with 5 mg of levocetirizine (fig. 1d).

We also evaluated the effect of levocetirizine on itch intensity. Both doses of levocetirizine suppressed itch intensity (fig. 2a). At early (1 h) and late (24 h) time points, the high dose of levocetirizine was more effective than the conventional dose (fig. 2a). We next examined adverse effects, using the Japanese version of the Epworth Sleepiness Scale (JESS) [8]. The double-dose group had a tendency toward drowsiness compared with the conventional-dose group. However, there was no significant difference in drowsiness between these two groups (fig. 2b).

Discussion

Management of CU includes H₁ antihistamines, sometimes at high doses, alone and in combination with H₂ antihistamines, leukotriene modifiers or other adjunctive agents such as cyclosporin A, dapsone and omalizumab [3, 9]. Although antihistamines are the mainstay for treatment of CU, many patients do not exhibit a good response to therapy with antihistamines, even at high doses [1, 3, 6, 10]. In addition to histamine released from skin mast cells, basophils and IgE may play a role in the pathogenesis of CU [3, 9]. Therefore, a combination of antihistamine and other drugs, such as the IgE monoclonal antibody omalizumab, may be effective in treating refractory urticaria. Doses of second-generation antihistamines as high as 4 times the recommended dose are advocated in international guidelines on CU [1, 3, 10]. However, only a limited number of published studies evaluating this approach have demonstrated a clear increase in efficacy [6].

Levocetirizine is classified as a nonsedating second-generation antihistamine. This drug performs suppressive functions on pruritus that is accompanied by urticaria [5]. In this study, we found that a double dose suppressed histamine-induced flare formation more rapidly and sustainably, and wheal and itch more extensively, compared with the conventional dose. Levocetirizine is known to exhibit better H₁ receptor occupancy in vivo 24 h after intake than desloratadine and fexofenadine [11]; however, the receptor occupancy of levocetirizine is still 57%. Although it remains unclear whether the inhibition by a double dose

only contributes to the H₁-receptor antagonistic response or not, we assume that the inhibition by a double dose is mostly due to the H₁-receptor antagonistic effect. Possible side effects with a double dose of levocetirizine include drowsiness, nasopharyngitis, fatigue and dry mouth. Especially drowsiness was reported to occur in a dose-response manner [11]; however, there was no significant difference in drowsiness between these two groups.

In addition, we evaluated the effects of antihistamines objectively, using both visual and LDI scales in a noninvasive manner. These findings support the rationale for increasing the dosage of nonsedating antihistamines in patients who do not respond to the conventional posology recommended by European guidelines [1, 3]. The limitations of the present study are the small number of enrolled participants and the dosage of the drug (only two doses). In addition, a histamine-induced skin reaction test was performed only in healthy donors. It would be of interest to apply this study to patients with refractory CU. Although such study limitations exist, these results suggest that a double dose of levocetirizine suppresses histamine-induced skin symptoms more rapidly, profoundly and sustainably than a conventional dose of levocetirizine.

Acknowledgments

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