

Effects of Bepotastine and Fexofenadine on Histamine-Induced Flare, Wheal and Itch

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Key Words

Bepotastine besilate • Fexofenadine hydrochloride •
Histamine • Pruritus • Urticaria

Abstract

Background: Urticaria is mainly caused by mast cell-derived histamine through the histamine H₁ receptor. Antihistamines are occasionally used on demand upon a recurrence of urticaria; therefore, rapidly acting agents should be explored. The onset of action is assumed to depend on time to maximum concentration (T_{max}), but the speed of action needs to be evaluated not only through blood concentration analysis but also by measuring in vivo effectiveness. **Methods:** In this study, we chose two representative second-generation antihistamines (bepotastine and fexofenadine) with relatively short T_{max} values and evaluated their effects on histamine-induced skin responses using both visual and laser Doppler imaging scales. **Results:** Suppression of histamine-induced flare and itch was observed 3 and 6 h after administration of both antihistamines. Attenuation of itch was seen 30 min after the administration of each drug and thereafter until 6 h. In addition, bepotastine suppressed flare formation after only 30 min following application. **Conclusion:** These results suggest that antihistamines suppress histamine-induced itch and flare, followed by wheal formation,

and that bepotastine suppresses skin symptoms sooner after administration than fexofenadine does, which is relatively consistent with the T_{max} results.

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Introduction

Histamine is released from skin mast cells to produce flare and wheal with pruritus by acting on blood vessels and sensory nerves [1, 2] and to modulate inflammatory conditions by acting on keratinocytes and other cells [3–9]. Oral antihistamines are the first-line treatment for urticaria, and their efficacy, speed and duration of action, as well as side effects, such as sleepiness and sedation, depend upon the propensity of each drug [1, 2].

Antihistamines are occasionally used on demand upon a recurrence of urticaria; therefore, rapidly acting agents should be explored. The onset of action is assumed to depend on time to maximum concentration (T_{max}), but the speed of action needs to be evaluated not only through blood concentration analysis but also by measuring in vivo effectiveness. In this study, we evaluated the suppressive effect and speed of action of antihistamines on histamine-induced skin response using iontophoresis.

Materials and Methods

This study was performed as a randomized, double-blinded, placebo-controlled, crossover trial on 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 ethic committee approved this study, and informed written consent was obtained from all participants.

Histamine dihydrochloride (Wako Pure Chemical Industries Ltd., Tokyo, Japan) was dissolved in distilled water at concentrations 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 placebo or antihistamines were administered. The maximum (r1) and orthogonal diameters (r2) were visually measured and the flare and wheal areas were calculated as $r1/2 \times r2/2 \times 3.14$. 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 using the manufacturer's software [10].

Responses to the test stimuli were assessed before and at 30 min, 3 and 6 h after administration of medication. Two second-generation antihistamines known for their short T_{max} values were selected: 10 mg of bepotastine besilate (Talion, Mitsubishi Tanabe Pharma Co. Ltd., Osaka, Japan; T_{max} 1.2 h) and 60 mg of fexofenadine hydrochloride (Allegra, Sanofi-Aventis Pharma, Frankfurt, Germany; T_{max} 2.6 h) [11, 12]. These drugs were administered orally to each healthy volunteer in a randomized order. A washout period of at least 1 week was maintained 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 (AUC) of ratings for 10 min (minimum 0, maximum 610) was calculated for analysis.

Results

Histamine iontophoresis induced wheal and flare, which persisted for at least 6 h in all volunteers (fig. 1, 2). The sizes of histamine-induced flare were comparable between bepotastine and fexofenadine before antihistamine administration (fig. 1a). At 3 and 6 h after antihistamine treatment, these two drugs significantly suppressed flare areas compared to placebo treatment, and there was no significant difference in the flare size between these two groups (fig. 1a, 2a). At 30 min after administration, fexofenadine did not suppress the flare response, yet bepotastine suppressed the flare size signifi-

cantly (fig. 2a). Similar results were obtained when the flare sizes were evaluated using LDI (fig. 2c). On the other hand, both of the drugs suppressed the wheal response at 3 and 6 h, but not at 30 min after treatment (fig. 2b). In addition, the wheal development at 3 and 6 h after administration was more significantly suppressed by bepotastine than by fexofenadine (fig. 2b).

We also evaluated the effect of antihistamines on itch intensity. Histamine-induced pruritus was suppressed by both antihistamines 30 min after administration, and the inhibitory effect was more prominent 3 and 6 h after the administration (fig. 3). The intensity of their inhibitory effects was comparable for both bepotastine and fexofenadine.

Discussion

In this study, we have demonstrated that antihistamines suppressed flare formation resulting from the iontophoresis of histamine 3 and 6 h after treatment, but only bepotastine significantly decreased flare formation 30 min after treatment. Wheal formation was inhibited by both antihistamines 3 and 6 h after treatment, and the inhibitory effect was more pronounced in the case of bepotastine. In addition, the anti-pruritic effect of both antihistamines was observed 3 and 6 h after treatment.

Bepotastine and fexofenadine are second-generation antihistamines with short T_{max} values and possess suppressive functions on pruritus that is accompanied by urticaria and atopic dermatitis, as well as on allergic reactions, especially in the nose, eye and skin [12–15]. The onset is supposed to depend on T_{max} , but it needs to be evaluated not only by blood concentration analysis but also by measuring in vivo effectiveness. Both bepotastine and fexofenadine significantly suppressed flare and wheal areas 3 and 6 h after treatment, but only bepotastine suppressed flare response 30 min after administration. One possible explanation for the rapid effect of bepotastine on inhibiting flare formation lies in the pharmacokinetic profile of these drugs. Bepotastine shows good absorbability compared with other antihistamines, with a T_{max} value in plasma of about 1.2 h in humans [11], which is shorter than that of fexofenadine [12]. On the other hand, there was no difference in the onset of suppressive effects on wheal formation and itch between these two drugs. T_{max} may be more directly reflected in flare rather than in wheal or itch. Another possible explanation for the rapid effect of bepotastine on inhibiting

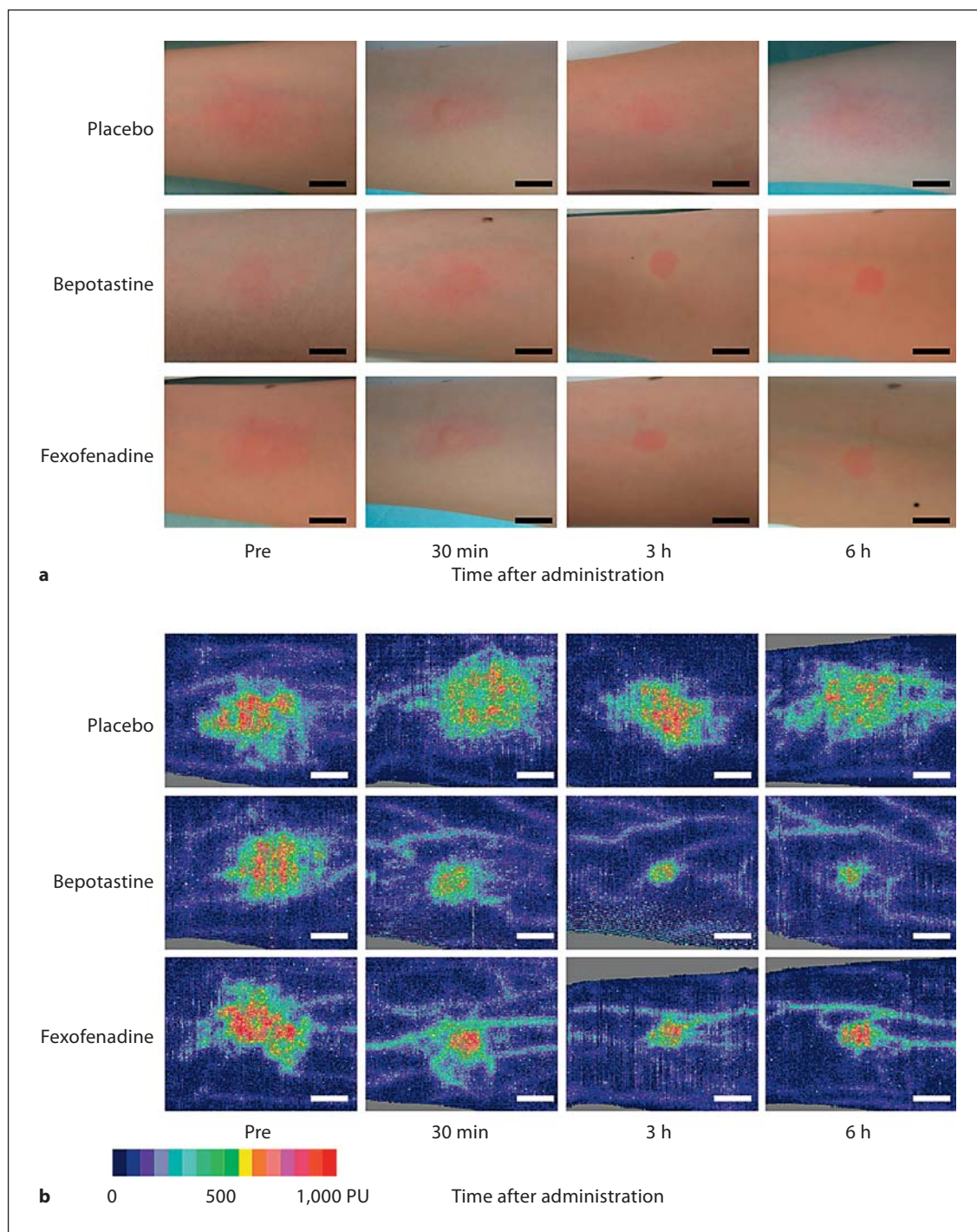


Fig. 1. Clinical images of histamine-induced flare and wheal. Pre = Before administration. **a** Clinical appearances. Representative clinical photos of histamine-induced flare and wheal at indicated time points after placebo, bepotastine and fexofenadine. Scale bars = 5 mm. **b** Scanning LDI taken at indicated time points. PU = Scanning laser Doppler perfusion units. Scale bars = 5 mm.

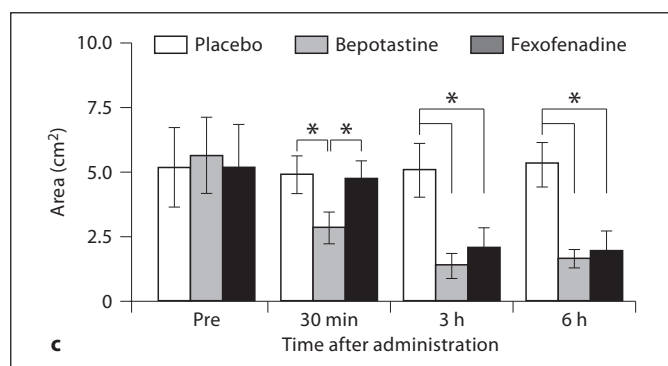
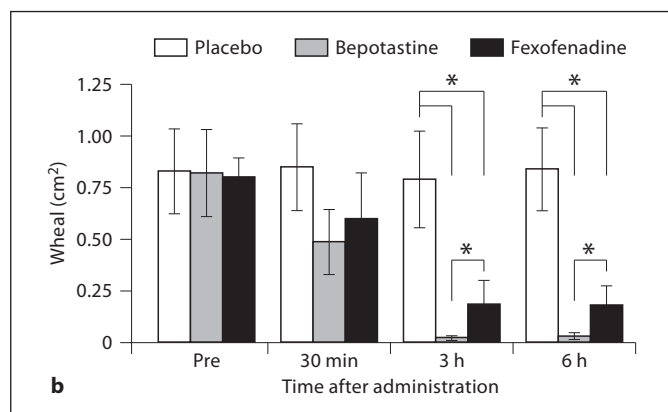
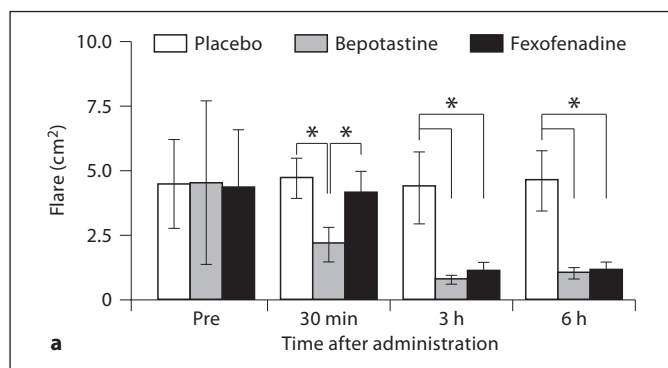


Fig. 2. Evaluation of antihistamines on histamine-induced flare and wheal responses. Pre = Before administration. **a** The flare size induced by histamine before and after administration. **b** The size of wheal induced by histamine before and after administration. **c** The area of flares evaluated by LDI. Placebo, bepotastine and fexofenadine are shown ($n = 10$). Results are presented as the mean $\pm$ SD. * $p < 0.05$ between the indicated groups by Tukey's nonparametric multiple comparison test.

flare formation is that flare is induced by increased blood flow arising from the induction of an axon reflex that is, for example, mediated by substance P [16]. And intriguingly, substance P-induced skin responses were suppressed by bepotastine [17].

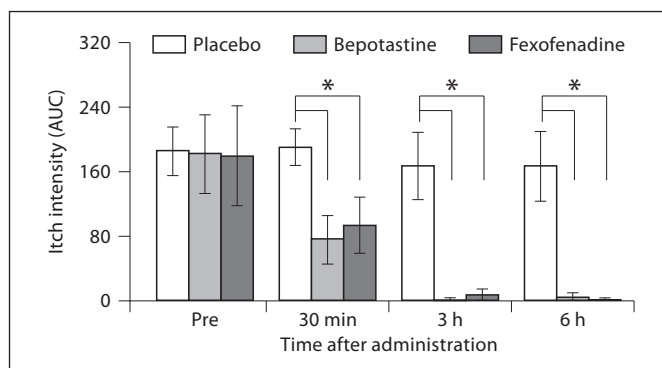


Fig. 3. The AUC of itch sensation induced by histamine iontophoresis. The AUC of itch intensity. Placebo, bepotastine and fexofenadine are shown ($n = 10$). * $p < 0.05$ between the indicated groups by Tukey's nonparametric multiple comparison test. Pre = Before administration.

In this study, we evaluated the effects of antihistamines on histamine-induced skin responses using both visual and LDI scales. When it comes to flare formation, similar findings were observed using visual scale and LDI. Since LDI is a non-invasive technique, this might be a suitable objective measurement of blood flow in the skin's microcirculation rather than visual evaluation.

Suppression of histamine-induced flare and itch was observed 3 and 6 h after administration of both antihistamines. Attenuation of itch was seen 30 min after the administration of each drug. In addition, bepotastine suppressed flare formation after 30 min following application. The limitations of the study are the number of applicants enrolled ($n = 10$), dosage of the drug and choice of comparator. In Western countries, fexofenadine is commonly applied at 120–180 mg daily, but in our country, we use fexofenadine 60 mg twice a day. Therefore, it would be informative to evaluate the dose response of fexofenadine in histamine-induced skin responses in the future. Although there exist a limitation of the study, these results may suggest that bepotastine suppresses skin symptoms sooner after administration than fexofenadine does, which is relatively consistent with the T_{max} results.

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