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ORIGINAL PAPER

Evaluation of the antihistamine effects of olopatadine, cetirizine and fexofenadine during a 24 h period: a double-blind, randomized, crossover, placebo-controlled comparison in skin responses induced by histamine iontophoresis

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Abstract Potency of the antihistamine effects of olopatadine, cetirizine and fexofenadine in standard-dose application were compared from 11.5 to 24 h after application. The test was designed in a double-blind, randomized, crossover, placebo-controlled study of ten healthy volunteers on histamine-induced flare and wheal response using an iontophoresis technique. The suppressive effect of olopatadine on the wheals induced by a 0.1-mA histamine iontophoresis lasted for 24 h after dosing. Fexofenadine administered using the same regimen was the least effective among three drugs tested. Suppression of the wheal response by cetirizine, taken once-daily, decreased with time. Olopatadine completely suppressed even the wheal response induced by a 0.2-mA histamine iontophoresis, although fexofenadine and cetirizine were less effective on the wheals induced by the same histamine challenge. There were no significant differences in subjective drowsiness and objective cognitive function between drug- and placebo-treated subjects. These results demonstrate that olopatadine is the most potent antihistamine among the three H_1-blockers when administered in a standard dosage.

Keywords Histamine iontophoresis · Wheal · Flare · Second-generation antihistamines · Olopatadine · Objective cognitive function

Introduction

Histamine is one of the important mediators that elicit a variety of symptoms such as an itch and the wheal response. Since these histamine-related symptoms provoke the urge to scratch, often impairing the quality of life, measures to suppress and control these symptoms are required. Second-generation antihistamines currently used to improve such symptoms are expected to exert potent clinical efficacy for 24 h, as itch or urticaria does not always occur at specific times of the day. Antihistaminic properties vary among the antihistamines depending on their binding ability to histamine receptors and their pharmacokinetics. These antihistamines can be administered once-daily or twice-daily depending on the patient's life style. However, there is concern with both regimens that the antihistamine effect might not be potent enough and therefore might dissipate before the next administered dosage.

The efficacy of second-generation antihistamines have been evaluated with histamine challenge tests using iontophoresis [1, 4, 5, 8]. Iontophoresis is a non-invasive method of histamine application used to induce an inflammatory skin response (wheal/flare). It is a reliable and useful test used to compare the antihistamine effects of different drugs. In former studies, suppression of the wheal/flare by second-generation antihistamines has been measured within the first 12 h after the initial dose, providing information on the relatively early phase of antihistamine efficacy [1, 4, 5, 8]. Few studies have evaluated the effects of antihistamines 24 h after the administration of a typical dose.

We compared the antihistamine effects of the commonly used second-generation antihistamines cetirizine hydrochloride (administered once-daily), olopatadine hydrochloride (administered twice-daily) and fexofenadine hydrochloride (administered twice-daily) in healthy subjects using the iontophoresis technique. This study evaluated the potency and duration of the antihistamine effects in accordance with the current manufacturer's recommended doses. The

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suppression of histamine-induced skin responses were measured at three-hour intervals after the first dose, from 11.5 to 24 h.

Skin symptoms in urticaria are largely different among individuals. Histamine concentrations in the wheal response are reported to be between 1,500 and 5,000 nM [6], thus showing a wide range of tissue concentrations. It is likely that histamine is released in very high concentrations in the lesions of patients with severe symptoms. The efficacy to inhibit the wheals induced by such a high release of histamine is one reason to administer antihistamines. In a previous study, larger histamine doses delivered by iontophoresis induced bigger wheals/flares [2]. We therefore compared the drugs in terms of their suppressive effects on severe wheals/flares, which were induced by a high histamine dose using iontophoresis applied at 0.2 mA, in addition to the usual test at 0.1 mA.

Materials and methods

Subjects

A total of 10 healthy adult volunteers (four men and six women) aged 20–28 years (mean 21.7) participated in the study. Subjects were excluded if they had taken any drug that had antihistamine action or any corticosteroid (oral/topical) within seven days prior to participation. The study was approved by the Medical Ethics Committee, School of Medicine, Shimane University (Approval No. 242), and all subjects gave written informed consent prior to participating.

Study design

A double-blind, randomized, crossover, placebo-controlled protocol was used. Testing for each treatment was separated by a washout interval of at least 7 days. The study design and evaluation with histamine iontophoresis is shown in Fig. 1. Subjects received active or placebo treatment at 21:00 and at 9:00 the following morning. The dosing schedule was as follows: olopatadine 5 mg twice-daily, cetirizine 10 mg once-daily and fexofenadine 60 mg twice-daily. For cetirizine the first dose was active and the second placebo. A pantethine 30 mg formulation (pantetheine) was used as a placebo. Olopatadine, cetirizine and fexofenadine were put into commercially available opaque gelatin capsules by a controller who was not involved in the wheal/flare measurement. The capsules were swallowed along with water. The controller made the treatment assignment and kept the key code until it was opened after the study was complete.

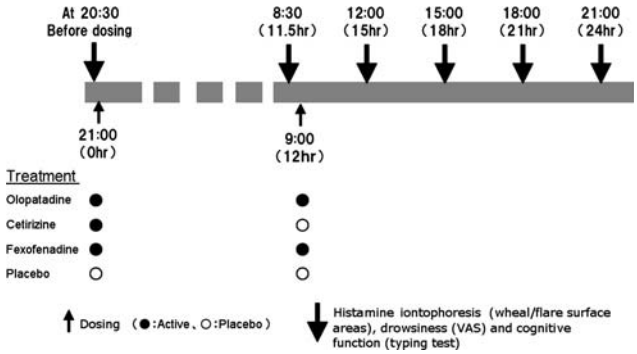

Fig. 1 Study design. Each subject was given for four kinds of treatment. Each treatment was separated by a washout interval of at least seven days. Measurement of the wheal/flares areas induced by histamine iontophoresis, assessment of drowsiness (VAS) and objective cognitive function (typing test) were performed before administration and at 11.5, 15, 18, 21 and 24 h after administration

Histamine-induced wheal/flare response

Histamine prepared as a 1% solution was administered on the volar surfaces of the forearms using an iontophoreser (UI-2060, BS Medical, Tokyo) [4]. The electrode had a tip diameter of 10.0 mm. Current was applied for 60 s at 0.1 mA to the right arm and at 0.2 mA to the left. Iontophoresis was performed at 0 (before dosing), 11.5, 15, 18, 21 and 24 h after the first dose was given. After 15 min, wheal/flare areas were traced onto a thin transparent plastic sheet, and the area was measured using "Image J" software.

Effects on drowsiness

Subjective drowsiness was evaluated by visual analog scale (VAS). Assessments were undertaken at 0 (before dosing), 11.5, 15, 18, 21 and 24 h after the first dose. The VAS was graded from 0 (no drowsiness) to 100 (excessive drowsiness).

Effects on objective cognitive function

The effects on objective cognitive function were assessed based on typing speed and accuracy using a typing training software, "MIKA TYPE©" [10]. Assessments were undertaken at 0 (before dosing), 11.5, 15, 18, 21 and 24 h after the first dose. At each assessment, the numbers of characters typed and errors made per minute were recorded in triplicate and the mean values representing typing speed and accuracy were used for analysis.

Statistical analysis

Results are expressed as mean ± SE. Statistical comparison of drugs and placebo was performed by using the Tukey's method. Tests were two-sided with significance at the 5% level.

Results

Skin responses (0.1 mA)

Suppression of the 0.1-mA iontophoresis-induced wheals was compared between the drugs and the placebo (Fig. 2a). Compared with the placebo, cetirizine and olopatadine significantly suppressed the wheals at all time points (from 11.5 to 24 h after the first dose). Fexofenadine significantly suppressed the wheals compared to placebo from 11.5 to 21 h after the first dose but was not significant at 24 h.

Suppression of the wheal response from 11.5 to 24 h after the first dose varied among the drugs tested. Olopatadine completely suppressed the wheals from 15 to 24 h. Wheal areas were significantly larger with twice-daily fexofenadine than with the same regimen of olopatadine.

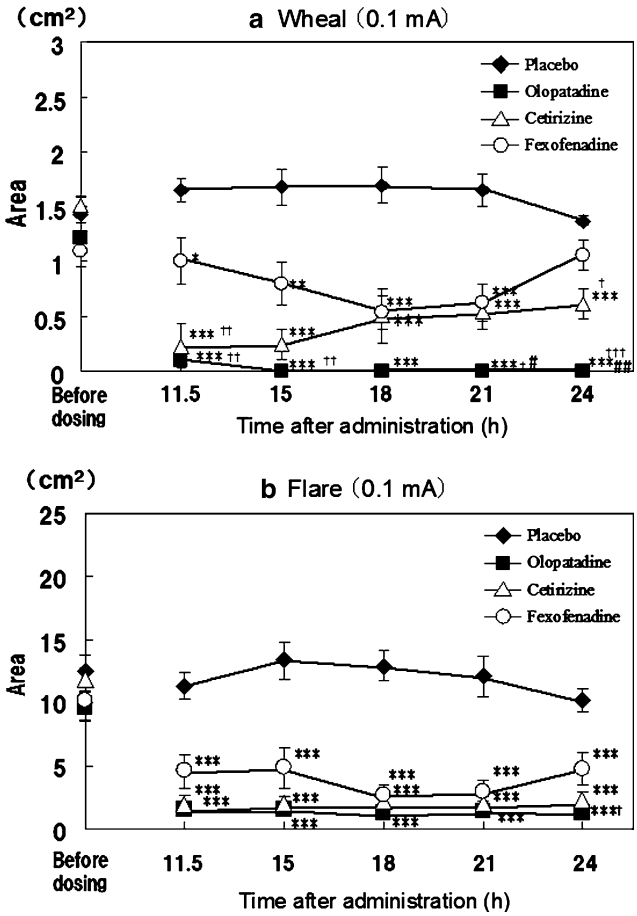

Fig. 2 Suppression of 0.1 mA iontophoresis-induced wheals (**a**) and flares (**b**) by antihistamines ($n = 10$). Data are presented as mean ± SE. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ vs placebo; $^{\dagger}P < 0.05$, $^{\dagger\dagger}P < 0.01$, $^{\dagger\dagger\dagger}P < 0.001$ vs fexofenadine; $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ vs cetirizine

Wheal suppression by cetirizine began to decline at 18 h, resulting in a significant difference from olopatadine in wheal area after 21 h.

Compared with the placebo, olopatadine, cetirizine and fexofenadine significantly suppressed the flares up to 24 h (Fig. 2b). Among these drugs the only significant difference exhibited at 24 h was between olopatadine and fexofenadine.

Skin responses (0.2 mA)

Suppression of the 0.2-mA iontophoresis-induced wheals was also compared between the administered drugs and the placebo (Fig. 3a). Compared with the placebo, only olopatadine and cetirizine significantly suppressed the wheals after 11.5 h. Fexofenadine-induced suppression was significant only at 15 and 21 h.

Although the histamine load had been increased with the 0.2 mA current, olopatadine completely suppressed the wheals from 15 to 24 h after the first dose with 0.1 mA induction. Olopatadine was significantly superior to fexofenadine throughout the study period. Wheal suppression by cetirizine began to decline at 15 h, showing a significant difference from olopatadine from 18 to 24 h.

Compared with the placebo, all the three drugs significantly suppressed the flares at all intervals (Fig. 3b). The significant difference was not shown in each administered drug.

Drowsiness

Subjective drowsiness assessed by VAS at specified times showed no significant differences between the placebo and the three administered drugs as shown in Fig. 4.

Objective cognitive function (typing test)

The typing test was performed to evaluate the effects of the antihistamines on cognitive performance. No significant differences were noted in typing speed between drugs and placebo at any time (Fig. 5a). As for typing accuracy, there were also no significant differences between the drugs and the placebo at any time (Fig. 5b).

Discussion

In this double-blind, randomized, crossover, placebo-controlled study, antihistamines were compared for the potency and duration of their antihistamine effects when administered in accordance with the manufacturer's recommended doses. The potency of antihistamine effect was assessed by measuring the histamine-induced wheal and flare areas. The

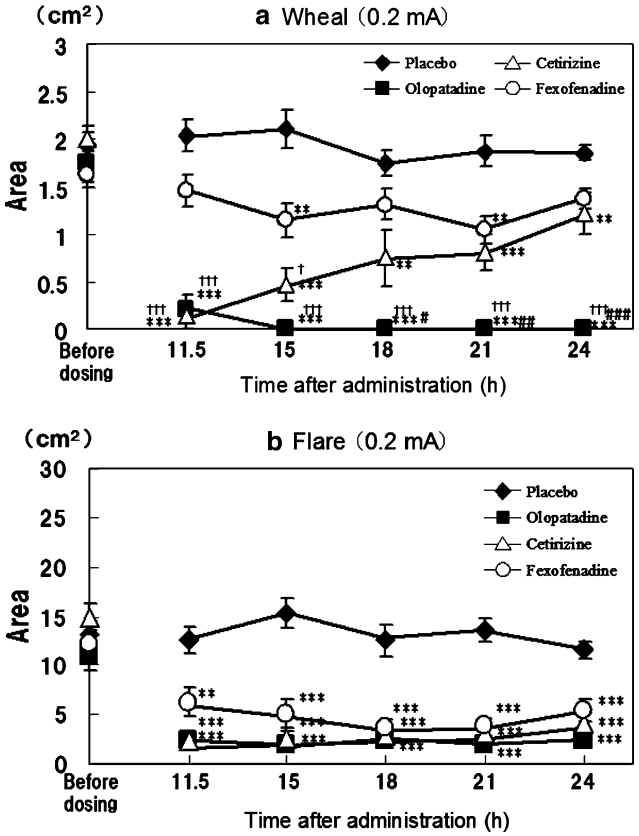

Fig. 3 Suppression of 0.2 mA iontophoresis-induced wheals (**a**) and flares (**b**) by antihistamines ($n = 10$). Data are presented as mean ± SE. $^{**}P < 0.01$, $^{***}P < 0.001$ vs placebo; $^{\dagger}P < 0.05$, $^{\dagger\dagger\dagger}P < 0.001$ vs fexofenadine; $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, $^{\#\#\#}P < 0.001$ vs cetirizine

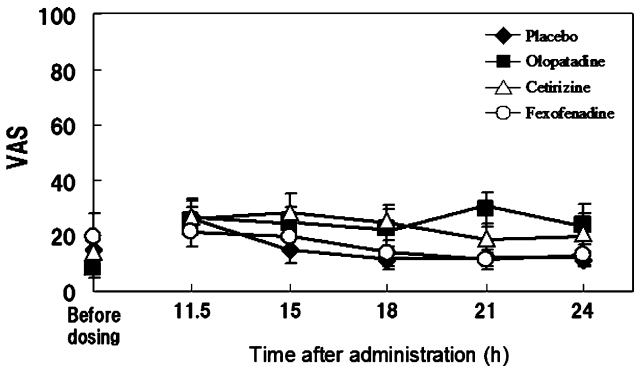

Fig. 4 VAS values of subjective drowsiness. Drowsiness was evaluated with VAS scores: 0 (no drowsiness) to 100 (excessive drowsiness) in 10 subjects. Data are presented as mean ± SE

duration of the antihistamine effect, up to next dosage, was determined by examining the wheals and flares at three-hour intervals from 11.5 to 24 h after the first dose. Among commonly used second-generation antihistamines, the once-daily formulation cetirizine and the twice-daily formulations olopatadine and fexofenadine were tested, taking into account the effects of dosing regimen on the duration

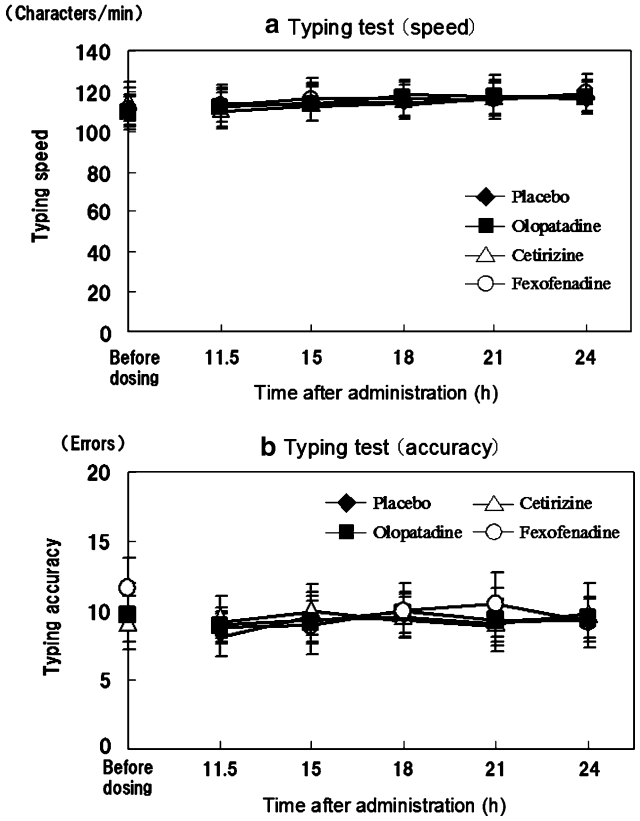

Fig. 5 Effects of antihistamines on subjective cognitive function. Typing speed (**a**) and typing accuracy (**b**) were evaluated with a typing training software in 10 subjects. Data are presented as mean ± SE

of action. Histamine challenge using a current of 0.2 mA was applied to obtain a model for severe symptoms. The three drugs were also evaluated for the potency and duration of the antihistamine effect.

All of the drugs proved to be effective in suppressing the flare response even to the high histamine challenge, while suppression of the wheal response varied among drugs. It is noteworthy that olopatadine completely suppressed the wheals induced by not only 0.1 mA but also 0.2 mA at and after 15 h, after the first dose. Fexofenadine administered twice-daily yielded significantly larger histamine-induced wheal areas than olopatadine administered in the same way, and fexofenadine was found to be the least potent among the drugs studied. This indicates that the potency and duration of antihistamine effects differ from drug to drug even within the same dosing regimen. There was a significant difference in the wheal suppression at and after 21 h between cetirizine given once-daily and olopatadine. Also cetirizine is likely to reduce its potency or become totally ineffective before the next dose is given in clinical practice.

The challenge tests with 0.2 mA histamine, providing models for severe symptoms, defined marked differences in suppression of the wheal response among drugs. Olopatadine

proved to be a potent antihistamine, since it completely suppressed over 15 h after the first dose with 0.1 mA induction. Fexofenadine-induced wheal suppression was not significantly potent or long-lasting compared with the placebo, suggesting that the drug administered according to the approved regimen is not potent enough for suppression of severe histamine-induced symptoms. The wheals were significantly larger with cetirizine than with olopatadine after 18 h, and the effect of cetirizine appears to decline at earlier phases after dosage in severe cases. These results indicate that adequate antihistamines should be prescribed for patients while considering the potency and duration of the antihistamine effect, especially in patients with severe symptoms.

The potent and long-lasting antihistamine effect of olopatadine may be related to the specific antagonistic activity of the drug. It has been reported that the inhibitory effect of olopatadine on histamine receptors is hardly reduced in the presence of high levels of histamine because of the antagonism noncompetitive [3]. We speculate that the twice-daily regimen also contributed to the potent antihistamine effect observed with olopatadine.

Antihistamines were less effective against wheal response than against flare response. Histamine with high concentrations is present in the wheal lesions; in fact it is reported that histamine concentration in skin necessary to induce a flare is 150–500 nM while 1,500–5,000 nM are required to induce a wheal [6]. Suppression of the wheal that contained higher concentrations of histamine required more potent antihistamines than did the flare in which histamine concentrations were relatively low.

Because of their pharmacological properties, antihistamines have side effects such as drowsiness and performance impairment. A drug which is expected to possess an antihistamine effect, potent and lasting for 24 h, would not be beneficial to patients if it causes drowsiness so severe as to negatively affect their daily life. In this study, there were no significant differences between drugs and placebo in the assessments of subjective drowsiness and objective cognitive function. As this study was primarily designed to evaluate the efficacy of the drugs during 24 h, assessments were not made at the time point when drug concentration in the blood reached a maximum (1.4 h after dose for cetirizine [7]; 1.0 hour for olopatadine [9], and 2.2 h for fexofenadine[1]). For olopatadine and fexofenadine, however, their twice-daily dosing schedule enabled us to assess drowsiness and cognitive function at three hours post-dose (15 h after the first dose). It is noteworthy that the assessments at this time point showed no significant differences between drugs and placebo, suggesting that drowsiness and performance impairment associated with medication are similar among the tested second-generation antihistamines. The second-generation antihistamines have less effect on the central nervous system than the first-generation antihistamines.

We found that the antihistamines administered in accordance with manufacturer's recommended doses were different with regard to potency and duration of action during a 24 h period. Of the drugs tested, olopatadine proved to be the most promising for its antihistamine effect, which was potent, stable and lasted for 24 h.

[1] Package insert of Allegra® tablets (Article in Japanese).

References

1. Estelle F, Simons R, McMillan JL, Simons KJ (1990) A double-blind, single-dose, crossover comparison of cetirizine, terfenadine, loratadine, astemizole, and chlorpheniramine versus placebo: suppressive effects on histamine-induced wheals and flares during 24 h in normal subjects. J Allergy Clin Immunol 86:540–547
2. Magerl W, Psych, D, Westerman RA, Möhner B, Handwerker HO (1990) Properties of transdermal histamine iontophoresis: differential effects of season, gender and body region. J Invest Dermatol 94:347–352
3. Matsumoto Y, Funahashi J Mori K, Hayashi K, Yano H (2007) The noncompetitive antagonism of histamine H_1 receptors expressed in Chinese hamster ovary cells by olopatadine hydrochloride: potency and molecular mechanism. Pharmacology (in press)
4. Morita K, Koga T, Moroi Y, Urabe K, Furue M (2002) Rapid effects of Olopatadine hydrochloride on the histamine-induced skin responses. J Dermatol 29:709–712
5. Morita E, Matsuo H, Zhang Y (2005) Double-blind, crossover comparison of Olopatadine and Cetirizine versus placebo: suppressive effects on skin response to histamine iontophoresis. J Dermatol 32:58–61
6. Petersen LJ, Churach MK, Skov PS (1997) Histamine is released in the wheal but not the flare following challenge of human skin in vivo: a microdialysis study. Clin Exp Dermatol 27:284–295
7. Sasa M, Naito M, Kojima T (1995) Pharmacokinetics of single and multiple doses of a new antiallergic drug, cetirizine, and examination of its safety. Jpn J Clin Pharmacol Ther 26:509–522
8. Takahashi H, Ishida-Yamamoto A, Iizuka H (2004) Effects of bepotastine, cetirizine, fexofenadine, and olopatadine on histamine-induced wheal- and flare-response, sedation, and psychomotor performance. Clin Exp Dermatol 29:526–532
9. Tsunoo M, Momomura S, Masuo M, Iizuka H (1995) Phase I clinical study on KW-4679, an antiallergic drug—safety and pharmacokinetics in the single and repeated administration study to healthy subjects. Kiso To Rinsho 29:4129–4147
10. Urae A, Okada M, Irie S, Tanaka T, Sunai Y, Niu S, Matsukuma K, Furue H, Tsukikawa H, Nitta Y, Nishikawa M, Nakano S (2000) Effects of fexofenadine hydrochloride on psychomotor performance: comparison of impaired performance of word processor by fexofenadine hydrochloride with that by *d*-chlorpheniramine maleate in healthy volunteers. Jpn J Clin Pharmacol Ther 31:649–658