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Short communication

Comparison of the effects of levocetirizine and loratadine on histamine-induced wheal, flare, and itch in human skin

Background: This randomized, double-blind, crossover study compared the effects of the *R*-enantiomer of cetirizine, levocetirizine, with those of loratadine on the wheal, flare, and itch response to histamine in human skin.
Methods: Levocetirizine (5 mg), loratadine (10 mg), or placebo was taken orally 4 h before the intradermal injection of histamine (20 μl, 100 μM) or the control vehicle into the forearm skin of healthy volunteers. Flare areas were assessed by scanning laser Doppler imaging before and at 30-s intervals for a period of 9 min. Wheal areas were measured by planimetry at 10 min. Itch was scored every 30 s with a visual analogue scale.
Results: After placebo administration, the mean peak flare area was 23.01 ± 1.94 cm^2, the wheal area 248 ± 27 mm^2, and the cumulative itch score $28.8 \pm 4.6\%$ (mean ± SEM). Levocetirizine reduced the flare, wheal, and itch by 60%, 68%, and 91%, respectively (all $P < 0.001$, Student's *t*-test for paired data). The effects of loratadine were variable and not statistically significant.
Conclusions: Levocetirizine (5 mg) is a potent inhibitor of the effects of histamine in human skin with an efficacy that exceeded that of loratadine (10 mg) when single doses of the drugs were administered 4 h before the test.

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Key words: antihistamines; flare; itch; levocetirizine; loratadine; skin; wheal.

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Cetirizine and loratadine, both inverse agonists at the histamine H_1-receptor (1), are widely used to prevent the symptoms of allergic reactions, particularly in the nose, eye, and skin. Early studies using the histamine-induced skin wheal reaction showed both drugs to be effective antihistamines (2, 3), and numerous clinical trials have confirmed this (4, 5).

Cetirizine is a racemic mixture of equal quantities of *S*- and *R*-enantiomers, and the *R*-enantiomer, levocetirizine, carries the majority of the histamine H_1-receptor-blocking activity (6). To confirm this, we have assessed the effectiveness of a single dose of 5 mg levocetirizine, the amount of this isomer in the standard 10 mg dose of the racemic mixture, in inhibiting the wheal and flare response to histamine in human skin. A standard 10-mg dose of loratadine was used as positive control and matching placebo as negative control.

Material and methods

The study was performed as a randomized, double-blind, placebo-controlled, crossover trial on 11 healthy volunteers with no history of allergy. The study was approved by the Southampton (UK) and South West Local Research Ethics Committee (study number 191/00), and all volunteers gave signed informed consent. Matching capsules of levocetirizine (5 mg), loratadine (10 mg), or placebo were taken orally 4 h before the start of each visit, and subjects were asked to refrain from eating, drinking caffeine-containing liquids, or taking excessive exercise for 2 h before attending the laboratory. As previous studies have shown that basal skin blood flow and vasoreactivity vary during the day (7–9), subjects were studied at the same time of day (between 1100 and 1300) in order to minimize intraindividual variation. All subjects were studied lying horizontally with their arms at heart level. Twenty microlitres of histamine (100 μM, UCB Pharma SA) or control vehicle (phosphate-buffered saline, PBS) was injected intradermally into the volar surface of the forearm, one injection per arm. Before and at intervals of 30 s for a period of 9 min after injection, changes in skin blood flow were assessed by scanning laser Doppler imaging (Moor Instruments Ltd, UK). Flare areas were calculated from the calibrated images with the manufacturer's software (10). The perimeter of the wheal at 10 min was traced onto an acetate sheet, and the area was calculated by planimetry. Itch sensation was scored every 30 s for a period of 10 min after histamine injection on a 10-cm visual analogue scale. All data are expressed as mean ± SEM, and statistical analysis was performed with Student's *t*-test for paired data. A probability value of $P < 0.05$ was taken as statistically significant.

Results

Intradermal injection of histamine caused a wheal and flare response in all volunteers, which was accompanied by the sensation of itch.

Analysis of the time course of the development of the

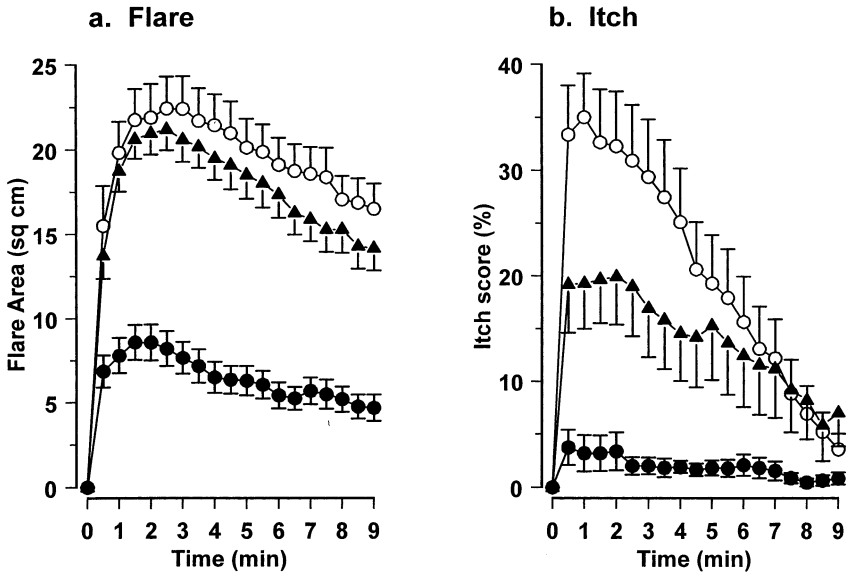

Figure 1. a) Flare and (b) itch responses to intradermal injection of 20 µl of 100 µM histamine. The drugs taken orally 4 h before histamine injection were placebo (open circles), 5 mg levocetirizine (closed circles), and 10 mg loratadine (closed triangles). Flare areas were computed from scanning laser Doppler images obtained every 30 s for 9 min. Itch was scored on a 10-cm visual analogue scale, and results were expressed as percentage of total. All data are mean ± SEM of results in 11 volunteers.

flare response (Fig. 1a), measured from the repeat scanning laser Doppler images, revealed that peak flare areas occurred 2–3 min after injection of histamine. Neither levocetirizine nor loratadine altered this time course. Fig. 2a shows that individual peak flare areas were consistently lower after levocetirizine dosing (9.1 ± 1.9 cm^2) than placebo (23.0 ± 1.9 cm^2, 60% reduction, $P < 0.001$). In contrast, the results after loratadine administration were very variable, the mean peak flare area of 21.4 ± 1.2 cm^2 being not significantly different from placebo. Intradermal injection of the saline vehicle caused a maximum flare area of 3.15 ± 1.4 cm^2, which was not significantly affected by drug administration. At 10 min, steady-state flare areas for placebo, levocetirizine, and loratadine were 14.6 ± 1.5 cm^2, 4.2 ± 0.7 cm^2 ($P < 0.001$), and 11.7 ± 1.3 cm^2 (not significant), respectively (Fig. 3).

The areas of the wheal responses assessed at 10 min were also consistently reduced by levocetirizine (Fig. 2b), the mean values being 248 ± 27 mm^2 for the placebo group and 80 ± 7 mm^2 after levocetirizine (68% reduction, $P < 0.005$). Loratadine again had a variable effect between subjects (Fig. 2b), the mean wheal area of 206 ± 29 mm^2 being not significantly different from placebo.

As may be seen in Fig. 1b, intradermal injection of histamine induced a marked itch response which peaked at ~1 min after injection. As the itch response waned rapidly, comparative results (Fig. 2c) were calculated as the cumulative score up to 5 min, expressed as a percentage of the total possible itch score during this period. Levocetirizine inhibited the total itch score in all subjects, the mean score of 2.5 ± 0.9% representing a 91% reduction from the placebo score of 28.8 ± 4.6% ($P < 0.001$). After loratadine administration, there was a marked reduction in the itch score in 5/11 individuals (Fig. 2c), but not in the remainder. The group mean score of 17.4 ± 4.2% was not significantly different from placebo.

Discussion

This study has shown that levocetirizine, the biologically active *R*-enantiomer of cetirizine, is a potent and consistent inhibitor of the wheal, flare, and itch responses resulting from the intradermal injection of histamine. While no direct "head-to-head" comparison has been made, the efficacy of a single dose of 5 mg levocetirizine in this study would appear to be at least equivalent to that of 10 mg of the racemic mixture (cetirizine) in other studies (10–14). This is consistent with the hypothesis that the antihistaminic effect of cetirizine resides in the levo-isomer, levocetirizine (6).

In comparison with the consistent inhibition of histamine-induced flare, wheal, and itch responses by levocetirizine, the effects of loratadine were variable, with the mean responses for the group failing to reach statistical significance. We have previously reported a similar weak and variable response with loratadine in comparison with cetirizine, using the same experimental protocol as in the current study (10). The finding of a weak and variable response with loratadine is also consistent with the reports of others (12–14). The reason for this variability of the efficacy of loratadine is not clear (Fig. 2). One explanation may lie in the pharmacokinetic profile of loratadine. Hilbert et al. (15) found

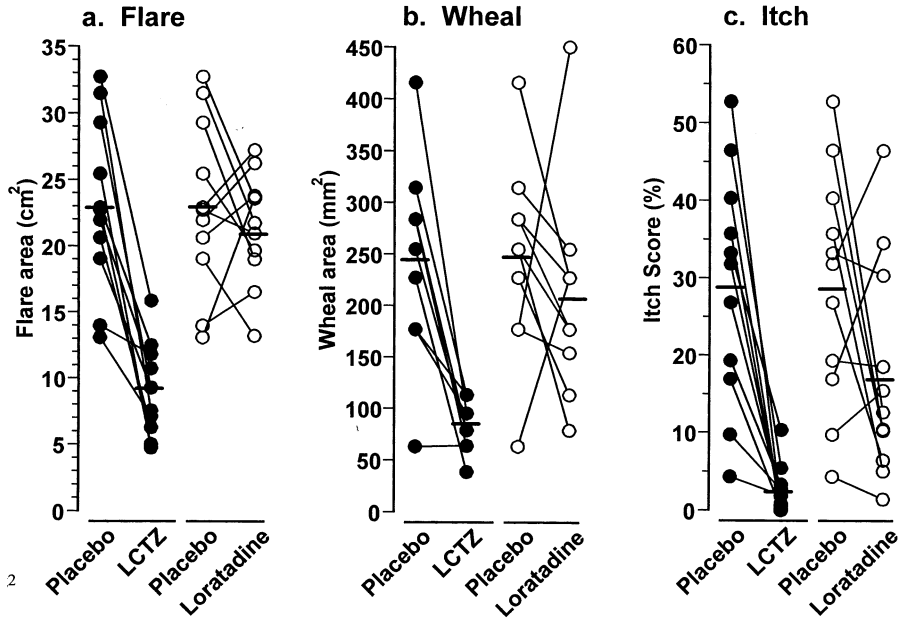

Figure 2. Individual a) flare, b) wheal, and c) itch responses to intradermal injection of 20 µl of 100 µM histamine. The drugs taken orally 4 h before histamine injection were placebo, 5 mg levocetirizine (LCTZ), and 10 mg loratadine. Peak flare areas were computed from scanning laser Doppler images. The 10-min wheal areas were determined by planimetry. Itch was scored on a 10-cm visual analogue scale, and results were expressed as percentage of total individual score up to 5 min. The horizontal lines indicate mean values for the 11 volunteers.

that peak plasma levels of loratadine occurred 1.5 h after oral dosage. The peak plasma level of descarboxyethoxyloratadine, the major metabolite of loratadine, which possesses 2.5–10 times the antihistaminic activity of loratadine in animal models (16, 17), also occurs in under 3 h (15). Thus, an interval of 4 h between dosing and testing should have been sufficient for absorption of loratadine and its metabolism to its more active form. However, delay in either may result in a variable test result in some individuals. Alter-natively, a single dose of 10 mg of loratadine was not high enough to inhibit the histamine-induced wheal, flare, and itch in all subjects.

In conclusion, a single 5-mg dose of levocetirizine has been shown to be an effective and consistent inhibitor of histamine-induced inflammation in the skin. In contrast, a single dose of 10 mg of loratadine afforded variable protection, being effective in some subjects, but not in others.

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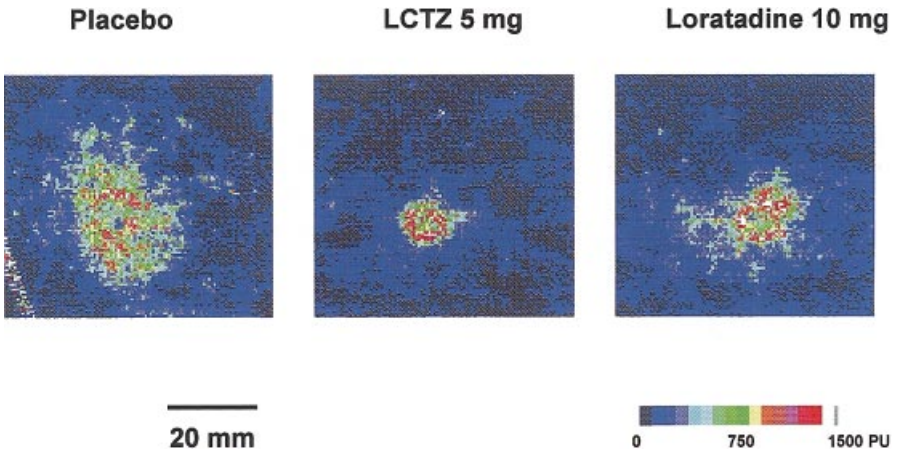

Figure 3. Scanning laser Doppler images taken at 10 min after intradermal injection of 20 µl of 100 µM histamine. The drugs taken orally 4 h before histamine injection were placebo, 5 mg levocetirizine, and 10 mg loratadine. The areas of the flares are 13.2, 3.0, and 9.8 cm^2, respectively. PU: scanning laser Doppler perfusion units.

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