Acta Derm Venereol 2013; 93: 286–293

INVESTIGATIVE REPORT

# The Inhibition by Levocetirizine and Fexofenadine of the Histamine-induced Wheal and Flare Response in Healthy Caucasian and Japanese Volunteers

Nicole SCHOEPKE, Martin K. CHURCH and Marcus MAURER
*Department of Dermatology and Allergy, Allergie-Centrum-Charité, Charité - Universitätsmedizin Berlin, Berlin, Germany*

**This randomized, double-blind, placebo-controlled crossover study compared inhibition by one 5 mg dose of levocetirizine with two 60 mg doses of fexofenadine separated by 12 h of histamine-induced wheal and flare responses in 9 Caucasian and 9 Japanese healthy male volunteers. Levocetirizine was more inhibitory than fexofenadine on wheal, flare and pruritus ($p < 0.005$). Variability, evaluated from the standard deviation of inhibition, ranged from 14% to 23.2% for levocetirizine and 65.4% to 112.4% for fexofenadine. Levocetirizine had a faster onset of action (30–90 min versus 2 h), shorter time to maximum effect (3–4 versus 3–6 h) and longer duration of action (at least 24 h versus ~12 h) than fexofenadine. The plasma levels of levocetirizine rose more quickly, reached higher levels, were more consistent and decreased slower than those of fexofenadine. There were no clinically significant ethnic differences in responsiveness to the drugs.** ***Key words: levocetirizine; fexofenadine; $H_1$-antihistamines; wheal and flare; Caucasian; Japanese; onset of action, duration of action*.**

Accepted Sep 10, 2012; Epub ahead of print Nov 13, 2012

Acta Derm Venereol 2013; 93: 286–293.

Professor Martin Church, Allergie-Centrum-Charité, Department of Dermatology and Allergy, Charité – Universitätsmedizin Berlin, Charitéplatz 1, DE-10117 Berlin, Germany. E-mail: mkc@soton.ac.uk

Levocetirizine and fexofenadine are both $H_1$-antihistamines with proven efficacy in the treatment of chronic spontaneous urticaria (1–4). While the best way to compare the clinical efficacy of both established and new drugs is to perform head-to-head studies, these are expensive and have ethical and logistical problems. From data examined in a recent review, especially the direct comparative data of desloratadine and levocetirizine in wheal and flare studies and chronic spontaneous urticaria, the wheal and flare model would appear to be the best indicator we have of effectiveness of $H_1$-antihistamines in urticaria (5).

Several previous studies have compared the effectiveness of single doses of levocetirizine and fexofenadine in suppressing histamine-induced wheal and flare responses. In 2002, Grant and colleagues (6) reported that single doses levocetirizine (5 mg) and fexofenadine (180 mg) were both effective within 1 h, had a similar maximum effectiveness but fexofenadine had a shorter duration of action. Another single dose study showed levocetirizine (5 mg) to be marginally more effective than fexofenadine (180 mg) (7) while a further study (8) reported that fexofenadine (180 mg) had a more rapid onset but a shorter duration of action than levocetirizine (5 mg).

While the dose of levocetirizine of 5 mg daily is the same in all countries, including Japan, this is not the case for fexofenadine. In Europe fexofenadine is marketed at 120 mg daily for the relief of symptoms associated with seasonal allergic rhinitis and 180 mg daily for the relief of symptoms associated with urticaria. However, in many other countries, including USA, Canada and Japan, fexofenadine is marketed at 60 mg twice daily for urticaria. In reviewing its effects in urticaria, Kawashima and colleagues (9) pointed out that in both studies in North America (10) and Japan (9) doses of 60 mg twice daily of fexofenadine significantly improved patient's quality of life. This was supported by a histamine-induced wheal and flare study in healthy Japanese volunteers which concluded that fexofenadine 60 mg twice daily was more effective than loratadine 10 mg once daily (11). Both studies suggested that it is unlikely that there are differences between the effectiveness of fexofenadine in Caucasians and Japanese individuals (9, 11).

However, to our knowledge, there are no reported comparisons of levocetirizine (5 mg) with fexofenadine 60 mg in wheal and flare studies. Consequently, the objective of this study was to assess the effects of a single 5 mg dose of levocetirizine with two 60 mg doses of fexofenadine given 12 h apart on histamine-induced pruritus and wheal and flare responses over a 24-h period and correlate them with plasma drug levels. The inclusion of both Caucasian and Japanese volunteers also allowed the exploration of possible ethnic differences.

## MATERIALS AND METHODS

### *Participants*

This was a randomized, double-blind, placebo-controlled three-way crossover study to compare the inhibitory effects of levocetirizine and fexofenadine in the histamine-induced wheal and flare and itch response. A total of 18 healthy male adult



© 2013 The Authors. doi: 10.2340/00015555-1490
Journal Compilation © 2013 Acta Dermato-Venereologica. ISSN 0001-5555

volunteers, 9 Caucasian (German) and 9 Japanese, (median age 26 years, range 21–34) were recruited by the Department of Dermatology and Allergy, Allergy Centre Charité, Charité, Universitätsmedizin Berlin. Power calculations from previous studies (6, 12) indicated that 18 individuals per group would be sufficient to show statistical significance with a 20% difference.

The exclusion criteria were a documented or suspected history of allergic disease or symptoms of acute or chronic disease. Oral antihistamines, antidepressants, antipsychotics or corticosteroids, aluminium and magnesium containing antacids, ketoconazole and erythromycin as well as topically applied antihistamines, corticosteroids or mast cell stabilizers were forbidden for 2 weeks prior to testing. Further, participants were forbidden to consume citrus fruits for 24 h before or during study days due to their possible effects on the absorption, distribution or metabolism of study drugs, particularly fexofenadine (13). Physical exercise was forbidden for 4 h prior to the skin prick testing.

The study was approved by the Ethics Committee of the Landesamt für Gesundheit und Soziales Berlin (EudraCT number: 2010-022747-38) and was conducted according to the Declaration of Helsinki and the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines, national laws and regulations as well as to the Standard Operating Procedures (SOPs) of the Allergie-Centrum of the Charité-Universitätsmedizin, Berlin. Its clinical trials.gov identifier number is NCT01586091.

Volunteers were informed about the study and a written informed consent was signed subsequently prior to enrolment. The data collected from each subject was recorded on a case report form (CRF) based on collected source data. The CRF was checked for completeness, consistency and plausibility by our study monitor. Recruitment began in February 2011, the first volunteer visit was on February 17, 2011 and the last volunteer visit was on October 24, 2011.

### *Study design*

The study design is shown in Fig. 1. Following an initial screening visit, all participants visited the department for three treatment visits. Treatment visits, which were of 24 h duration, were separated by a washout period of at least 6 days. The three treatments, given in random order, were: placebo at 0 h and at 12 h; levocetirizine 5 mg at 0 h and placebo at 12 h; and, fexofenadine 60 mg at 0 h and at 12 h. Tablets of fexofenadine hydrochloride 60 mg (Sanofi-Aventis Deutschland GmbH, Frankfurt am Main, Germany), levocetirizine dihydrochloride 5 mg (UCB GmbH, Monheim, Germany) and placebo, were contained in opaque capsules identical in shape, size and colour. Capsules were swallowed whole with water.

Volunteers were given a standard breakfast 1¼ h after taking the first drug dose and a dinner 1¼ h after administration of the second drug dose. Individuals were only allowed to drink during the intervening period. To control for circadian changes, all drugs were administered at similar time for each subject in each treatment period.

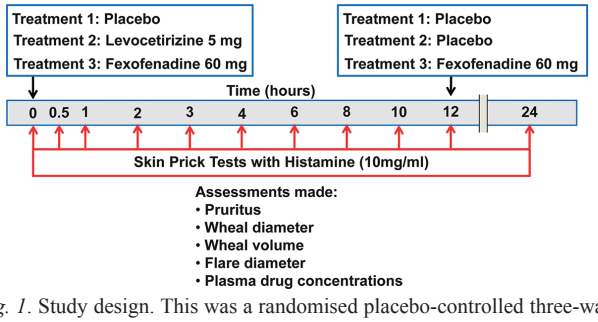


*Fig. 1.* Study design. This was a randomised placebo-controlled three-way crossover study with 6 days washout between visits. The participants were 18 healthy adult male volunteers, 9 Caucasian and 9 Japanese.

At each treatment visit, 5 ml venous blood samples were taken through a catheter inserted into the antecubital vein of the left arm, and skin prick tests (SPT) performed on the volar surface of the forearm using histamine 10 mg/ml (Bencard Allergie GmbH, München, Germany) 15 min before drug administration (baseline) and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12 and 24 h afterwards. Measurements made at each time point were as follows. Pruritus was assessed every 30 s for 10 min after SPT using a visual analogue scale (VAS) score with a "0" and "10" at the two extremes of an unmarked 100 mm line. The mean VAS for each 10 min was calculated and used as a primary end point. Wheal diameter was measured with a transparent ruler as the mean of the largest diameter and the diameter at right angles to this. Wheal volume (results in Fig S1; available from http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1490) was measured by a non-contact three dimensional measurement system (PRIMOS contact, GFM Messtechnik GmbH, Teltow, Germany). Flare diameter was measured with a transparent ruler as the mean of the largest diameter and the diameter at right angles to this. All these measurements were made 10 min after SPT. Plasma drug concentrations were measured in the venous blood samples, which had been taken into heparinized vials, centrifuged and stored at –18°C prior to assay, by Berliner Betrieb für Zentrale Gesundheitliche Aufgaben, Institut für Toxikologie, Klinische Toxikologie und Giftnotruf Berlin, Fachbereich Klinische Toxikologie und Pharmakologie.

### *Adverse events*

The occurrence of adverse events (AEs) was investigated by questioning and/or examination on each study day.

### *Statistical analyses*

Student's *t*-test for paired samples to compare the three study groups: placebo, fexofenadine and levocetirizine. As two independent variables were compared with one placebo value, $p < 0.025$ was accepted as a statistically significant difference (Bonferroni correction). The significance of the difference between the effectiveness of the two drugs was assessed by applying Student's *t*-test for paired samples to the difference between responses obtained after drug and placebo administration. As only comparisons of individual pairs were made, $p < 0.05$ was accepted as a statistically significant difference.

Because the maximum inhibitory response of different individuals occurred at different times, the mean of responses between 3 and 8 h was calculated in order to gain a measure of comparative efficacy of the two drugs at peak effect and to look for differences between the two ethnic groups. In addition, the mean percentage inhibition of placebo was calculated for the 24-h period. Again, Student's *t*-test for paired samples was used to calculate the significance of differences and $p < 0.05$ accepted as a statistically significant difference. Numerical data are shown as mean ± SEM. The statistical differences between the numbers of individuals with a ≥75% inhibitory response were calculated using Fisher's two tailed test. Spearman Rank correlation coefficients were used to investigate relationship between drug plasma concentrations and dermal responses.

## RESULTS

### *Participant demographics*

There was no significant difference in age between the 9 Caucasian men (25.4 ± 1.3 years) and the 9 Japanese

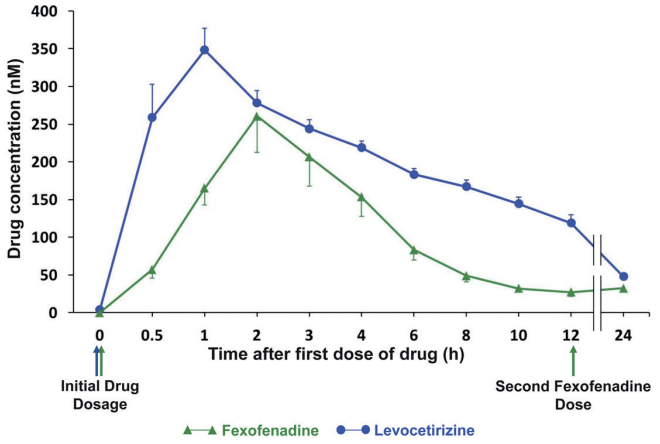


*Fig. 2.* Plasma levels of levocetirizine and fexofenadine. Levocetirizine was given as a single 5 mg oral dose at 0 h. Fexofenadine was given as two 60 mg oral doses, one at 0 h and the second at 12 h. Each point is the mean ± SEM of measurements in 18 individuals.

men (26.4 ± 1.0 years). The Caucasian men were significantly taller ($p = 0.01$) (1.80 ± 0.03 vs. 1.71 ± 0.02 m) and heavier ($p = 0.01$) (77.7 ± 3.6 vs. 64.4 ± 2.0 kg) than their Japanese counterparts. However, the values for body mass index (24.1 ± 1.2 vs. 23.1 ± 0.7) were not statistically different.

### *Plasma drug levels*

The plasma level of levocetirizine rose rapidly reaching a maximum of 348 ± 29 nM one hour after dosing (Fig. 2 and Table SI; available from http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1490). Although fexofenadine was given at a higher dose, it was more slowly absorbed into the systemic circulation and reached a maximum of only 260 ± 48 nM at 2 h. The difference between these levels was not statistically significant ($p = 0.077$). However, the slower systemic absorption and more rapid clearance of fexofenadine caused the mean area under the curve (AUC) for the 12 h after the initial dose (AUC 12 h) of 1,202 ± 190 nM to be less than half of the AUC 12 h of levocetirizine of 2,548 ± 84 nM ($p < 0.0001$). The levels of fexofenadine at 12 h and 24 h, 12 h after the second dose, of 27 ± 6 and 32 ± 3 nM, respectively, were not significantly different from each other ($p = 0.186$).

There were no significant differences between Caucasian and Japanese volunteers in either the mean peak levocetirizine levels of 313 ± 45 and 384 ± 32 nM ($p = 0.208$) and mean AUC 12 h of 2,500 ± 142 and 2,595 ± 86 nM ($p = 0.673$). Similarly, there were no significant differences between Caucasians and Japanese in either the mean peak fexofenadine levels of 198 ± 26 and 323 ± 91 nM ($p = 0.207$) and mean AUC 12 h of 907 ± 93 and 1,496 ± 354 nM ($p = 0.132$). The numerically higher mean fexofenadine levels in the Japanese men was primarily due to one individual who had a peak level at 3 h of 1,011 nM and an AUC 12 h of 4,221 nM, some 4 times greater than the median level of the other 8 individuals.

### *Pruritus*

Analysis of the pruritus data revealed that the mean VAS score of 3.03 ± 0.70 for Japanese men was more than three times higher than the mean score of 0.84 ± 0.22 for Caucasian men. This difference was statistically significant ($p = 0.031$).

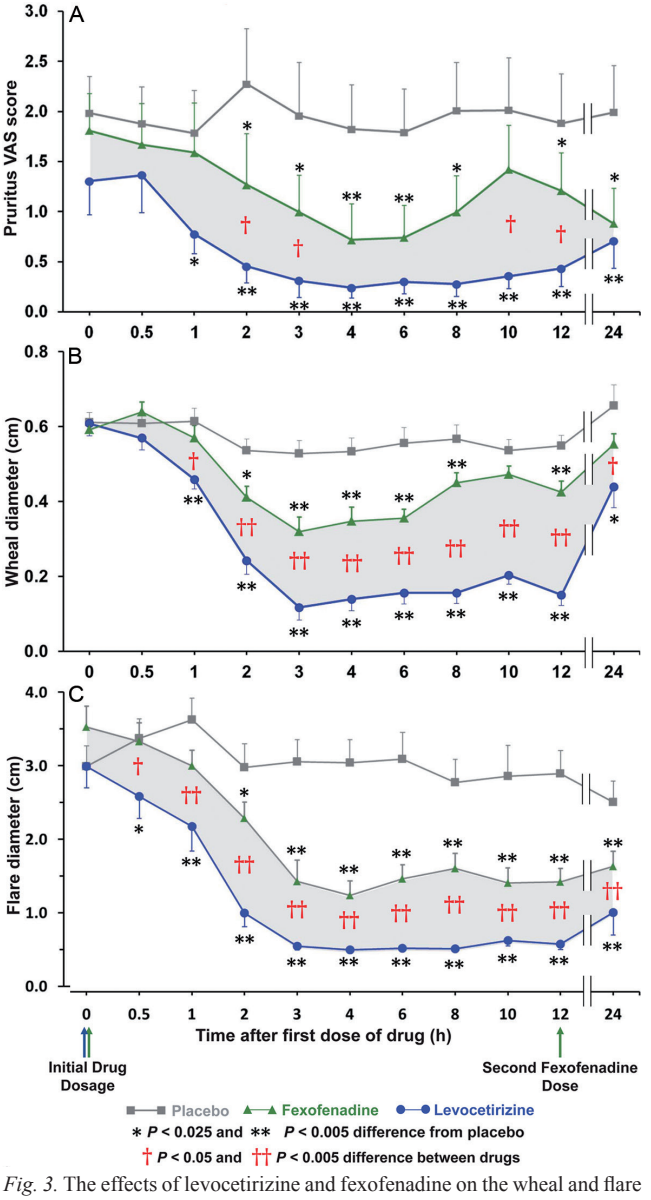


*Fig. 3.* The effects of levocetirizine and fexofenadine on the wheal and flare response. A) *Pruritus*: The severity of itching provoked by skin pricks with histamine (10 mg/ml) was recorded on a 10 cm VAS every 30 s for 10 min and the mean score for this period calculated. B) *Wheal diameter*: Wheals were provoked by skin pricks with histamine (10 mg/ml) and wheal diameter measured 10 min later. C) *Flare diameter*) Flares were provoked by skin pricks with histamine (10 mg/ml) and flare diameter measured 10 min later. Levocetirizine was given as a single 5 mg oral dose at 0 h. Fexofenadine was given as two 60 mg oral doses, one at 0 h and the second at 12 h. Each point is the mean ± SEM of measurements in 18 individuals.

Analysis of the whole 18 individuals showed that levocetirizine produced a significant ($p < 0.025$) inhibition of histamine-induced pruritus by 1 h and a highly significant ($p < 0.001$) inhibition thereafter (Fig. 3A and Table SII; available from http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1490). Fexofenadine produced significant ($p < 0.025$) inhibition at 2 h after dosing and highly significant ($p < 0.001$) inhibition only at 4 and 6 h. The peak effect of both drugs was seen at 4 h.

Calculation of the mean 3–8 h percentage inhibitions of pruritus showed that inhibition produced by levocetirizine of 83.3 ± 3.7% was statistically higher ($p = 0.003$) than that of the 56.1 ± 8.9% inhibition produced by fexofenadine. The mean percentage inhibition of pruritus over the complete 24 h observation period was 61.8 ± 12.5% for levocetirizine and 45.1 ± 8.6% for fexofenadine (N.S.). Despite the differences in the baseline VAS responses for itch between Caucasian and Japanese men, there were no significant differences between the ethnic groups in their responsiveness to either drug (Table I). Levocetirizine was significantly more effective than fexofenadine in the Japanese group ($p = 0.025$) but just failed to reach significance in the Caucasian group ($p = 0.066$) (Table I).

### *Wheal diameter*

There was no significant ethnic difference in the mean wheal diameters over the 24-h observation period following the administration of placebo, those of the Caucasian and Japanese volunteers being 0.53 ± 0.03 and 0.61 ± 0.02 cm, respectively.

Levocetirizine produced a highly significant ($p < 0.001$) inhibition of the histamine-induced wheal diameter from 1 to 12 h after dosing, which was still significant ($p < 0.025$) at 24 h (Fig. 3B and Table SIII; available from http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1490). Fexofenadine produced significant ($p < 0.025$) inhibition at 2 h after dosing and highly significant ($p < 0.001$) inhibition between 3 and 8 h. The peak effect of both drugs was at 3 h. Levocetirizine was significantly more effective than fexofenadine from 1 to 24 h after dosing.

Calculation of the mean 3–8 h percentage inhibitions from placebo wheal diameter showed that inhibition produced by levocetirizine of 73.5 ± 4.0% was statistically higher ($p < 0.0001$) than that of the 29.8 ± 4.9% inhibition produced by fexofenadine. The mean percentage inhibition of wheal diameter over the complete 24-h observation period was 53.1 ± 2.9% for levocetirizine and 18.6 ± 3.6% for fexofenadine ($p < 0.0001$).There were no significant differences between Japanese and Caucasian men in their responsiveness to either drug (Table I). Levocetirizine was significantly more effective than fexofenadine in both ethnic groups (Table I).

### *Wheal volume (see Fig. S1)*

### *Flare diameter*

The mean flare diameter over the 24-h observation period following the administration of placebo was 3.09 ± 0.26 cm. There were no significant ethnic differences, the mean flare diameters of the Caucasian and Japanese volunteers being 2.89 ± 0.39 and 3.35 ± 0.34 cm, respectively.

Levocetirizine produced a significant ($p < 0.025$) inhibition of flare diameter by 30 min and a highly significant ($p < 0.001$) inhibition of histamine-induced flare diameter thereafter (Fig. 3C and Table SV; available from http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1490). In contrast, fexofenadine produced a significant ($p < 0.025$) inhibition of flare

Table I. *Inhibitory effects of levocetirizine and fexofenadine in Japanese and Caucasian subjects*

| | Levocetirizine one 5 mg dose | Fexofenadine two 60 mg doses | Significance between the active medications |
|---|---|---|---|
| Pruritus (% inhibition) | | | |
| Caucasian ($n = 9$) | 77.8 ± 5.1 | 58.1 ± 11.6 | N.S. |
| Japanese ($n = 9$) | 88.8 ± 4.5 | 54.1 ± 12.8 | $p = 0.025$ |
| Significance between the ethnic groups | N.S | N.S | |
| Wheal diameter (% inhibition) | | | |
| Caucasian ($n = 9$) | 73.1 ± 7.5 | 21.3 ± 5.6 | $p < 0.0001$ |
| Japanese ($n = 9$) | 73.9 ± 2.7 | 38.4 ± 7.0 | $p = 0.002$ |
| Significance between the ethnic groups | N.S. | N.S. | |
| Wheal volume (% inhibition) | | | |
| Caucasian ($n = 9$) | 77.6 ± 7.2 | 23.0 ± 18.0 | $p = 0.002$ |
| Japanese ($n = 9$) | 84.1 ± 4.4 | 61.8 ± 8.4 | $p = 0.008$ |
| Significance between the ethnic groups | N.S. | N.S. | |
| Flare diameter (% inhibition) | | | |
| Caucasian ($n = 9$) | 76.8 ± 3.3 | 35.6 ± 10.7 | $p = 0.002$ |
| Japanese ($n = 9$) | 74.9 ± 7.0 | 53.8 ± 6.8 | $p = 0.001$ |
| Significance between the ethnic groups | N.S. | N.S. | |

The values in this Table are the mean ± SEM percentage inhibitions of the placebo response for the period 3–8 h after drug administration.

diameter at 2 h after dosing and had a highly significant ($p < 0.001$) effect throughout the rest of the observation period. The peak effect of both drugs was seen at 4 h.

Calculation of the mean 3–8 h percentage inhibitions from placebo flare diameter showed that inhibition produced by levocetirizine of 75.8 ± 4.0% was statistically higher ($p < 0.0001$) than that of the 44.7 ± 6.9% inhibition produced by fexofenadine. The mean percentage inhibition of flare diameter over the complete 24-h observation period was 62.3 ± 3.5% for levocetirizine and 32.5 ± 5.0% for fexofenadine ($p < 0.0001$).There were no significant differences between Japanese and Caucasian men in their responsiveness to either drug (Table I). Levocetirizine was significantly more effective than fexofenadine in both ethnic groups (Table I).

### *Individual responses*

The mean percentage inhibitions of pruritus, wheal and flare for each individual volunteer during the 3–8 h period after drug administration are shown in Fig. 4. The results for pruritus show that after taking levocetirizine, 13 of the 18 volunteers had a response ≥ 75% during this period, whereas after fexofenadine only 7 had a response of this magnitude. This difference was not significant ($p = 0.092$, Fisher's exact test). However, for reduction of wheal diameter, wheal volume and flare diameter, a significantly greater effect of levocetirizine was seen compared with fexofenadine (Fig. 4).

### *Variability of response*

The variability of plasma drug levels and dermal responses were determined by expressing the standard deviation as a percentage of the mean value (Table II). The results for the AUC (0.5–12 h) for plasma concentrations of drugs show 67% variability for fexofenadine levels, 4.8 times higher than the 14% variability of levocetirizine. Similarly, the variability of pruritus, wheal diameter, wheal volume and flare diameter were 3.5, 3.0, 4.8 and 2.9 times higher for fexofenadine than levocetirizine.

To investigate whether the variability of the dermal responses were related to the plasma concentrations of the drugs, the Spearman Rank correlation coefficients were calculated (Table II). For levocetirizine, there was no correlation between plasma drug levels and any of the dermal responses. However, for fexofenadine, there was a statistically significant correlation between plasma drug levels and wheal diameter, wheal volume and flare diameter suggesting their variability to be at least partially dependent on variable drug absorption.

### *Hysteresis loops*

When the percentage of suppression of wheal, flare or pruritus responses is plotted against the drug concentration in the plasma a counter-clockwise hysteresis loop results (14). Hysteresis loops for inhibition by levocetirizine and fexofenadine of the flare response are shown in Fig. 5. The loops for both drugs show clearly that while the drug concentrations in the plasma reached a maximum after 1–2 h, maximal inhibition of the flare occurred at 4 h. Furthermore, the inhibitory effects of the drugs were relatively well maintained even though the plasma concentrations fell to low levels.

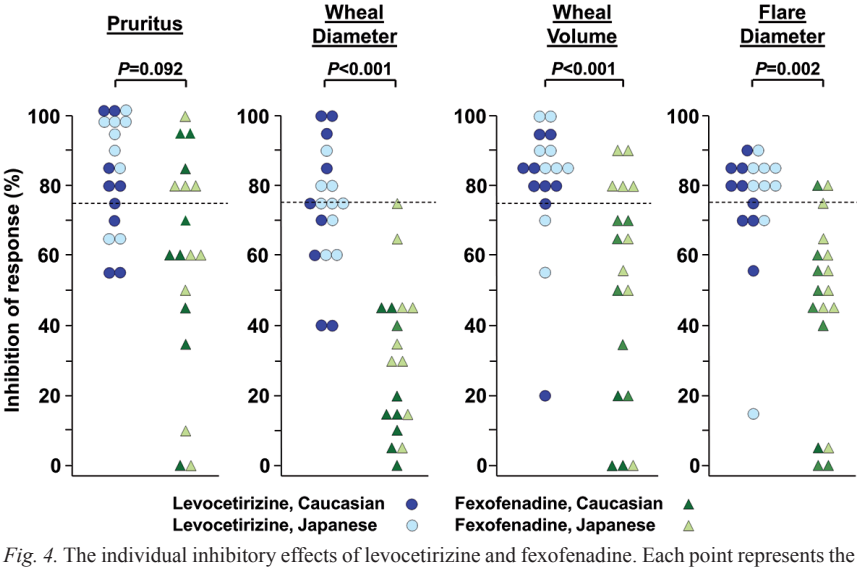


*Fig. 4.* The individual inhibitory effects of levocetirizine and fexofenadine. Each point represents the mean percentage inhibition of placebo responses from 3–8 h after dosing for each of the 18 volunteers. In order to improve the clarity of this figure, each value has been approximated to the nearest 5%. *p*-values refer to the difference between drugs in the numbers of individuals with a ≥ 75% inhibitory response. These were calculated using Fisher's two-tailed test.

### *Adverse events*

No severe adverse events or suspected unexpected serious adverse reactions occurred during this study. No volunteer withdrew from the study before its completion. Adverse events (AEs) were reported by 7 individuals. One individual reported fatigue on one study day after taking levocetirizine. This resolved within 24 h. Other AEs, which were probably not drug related, included pain at the puncture site of the intravenous catheter (2 individuals – 1 placebo and 1 fexofenadine), upper respiratory tract infection (3 individuals – 2 levocetirizine and 1 fexofenadine), bacterial inflammation of the finger (1 individual - fexofenadine) and pain in the knee joint (1 individual – placebo).

Table II. *Variability of plasma concentrations of levocetirizine and fexofenadine with percentage inhibitions from placebo for pruritus, wheal diameter, wheal volume and flare diameter*

| | Plasma concentration nM | Pruritus % inhibition | Wheal diameter % inhibition | Wheal volume % inhibition | Flare diameter % inhibition |
|---|---|---|---|---|---|
| *Levocetirizine* | | | | | |
| Mean | 2,547.5 | 83.3 | 73.5 | 80.9 | 75.8 |
| SD | 357.8 | 15.8 | 16.9 | 18.8 | 16.9 |
| SD % Mean | 14.0 | 19.0 | 23.0 | 23.2 | 22.3 |
| Spearman rank correlation with plasma concentration | | | | | |
| Coefficient | | 0.158 | 0.165 | 0.273 | 0.199 |
| Significance | | N.S. | N.S. | N.S | N.S |
| *Fexofenadine* | | | | | |
| Mean | 1,201.8 | 56.1 | 29.8 | 42.4 | 44.7 |
| SD | 804.4 | 37.8 | 20.9 | 47.6 | 29.3 |
| SD % Mean | 67.0 | 67.4 | 70.0 | 112.4 | 65.4 |
| Spearman rank correlation with plasma concentration | | | | | |
| Coefficient | | 0.251 | 0.478 | 0.558 | 0.519 |
| Significance | | $p=0.298$ | $p=0.047$ | $p=0.021$ | $p=0.031$ |

Plasma concentrations are the mean area under the curve values for 0–12 h after dosing. Values of pruritus, wheal diameter, wheal volume and flare diameter are the mean of percentage inhibition of placebo responses from 3–8 h after dosing for all 18 volunteers.

## DISCUSSION

This study showed that both a single 5 mg dose of levocetirizine and two 60 mg doses of fexofenadine given 12 h apart significantly reduced histamine-induced pruritus and wheal and flare responses over a 24-h period. In all parameters measured, levocetirizine was more rapid in onset and more effective while fexofenadine was more variable. There appeared to be no clinically relevant differences between Caucasian and Japanese volunteers in their responsiveness to the drugs.

Plasma concentrations of drugs following oral administration are dependent on the rate and degree of absorption, distribution and elimination. Levocetirizine is rapidly and effectively absorbed through the intestine (15), has a small volume of distribution (16) and is excreted into the urine following glomerular filtration and tubular secretion (17). The rapid absorption of levocetirizine, peaking at 1 hour at 348 ± 29 nM, and its clearance from the plasma with a half-life (t½) of approximately 8 h is consistent with its route of excretion (16, 18).

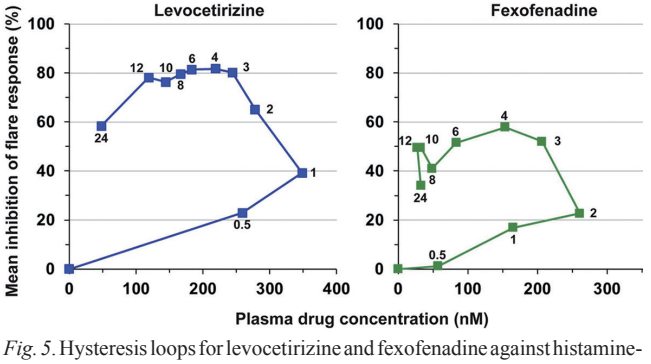


*Fig. 5.* Hysteresis loops for levocetirizine and fexofenadine against histamine-induced flare diameter. The numbers refer to time in hours after the first dose of drugs. Inhibitions of flare response were calculated from the mean diameters recorded from 18 individuals.

Although fexofenadine was given at a dose 12 times greater than that of levocetirizine, it was more slowly absorbed into the systemic circulation and reached a maximum of only 260 ± 48 nM at 2 h. Furthermore, its plasma levels were more variable than those of levocetirizine. By 12 h, fexofenadine had been almost completely cleared from the circulation. The plasma level of fexofenadine 12 h after its second administration was also very low and showed no significant accumulation. These results are consistent with a previous study (11). The pharmacokinetics of fexofenadine are complex. Unlike most other second generation $H_1$-antihistamines, fexofenadine has very low tissue permeability which severely limits its passive absorption through the intestinal wall (19). However, this process is augmented by active uptake via the organic anion transporting protein, OATP1A2, expressed on the luminal membrane of small intestinal enterocytes (20–22).

The genetic variability in genes encoding OATP transporters (21) and their inhibition by the grapefruit flavonoid naringin, and probably by other flavonoids in fruits and vegetables (23), results in marked inter-individual differences in the intestinal absorption of fexofenadine. In addition, OATP transporters, probably OAT1B3 (24), also facilitate the active hepatic uptake of fexofenadine from where it is pumped into the bile under the influence of the efflux transporter, P-glycoprotein (20). These active transporters, which facilitate the relatively rapid removal of fexofenadine from the blood, bring a second level of variability due to genetic differences and modulation by dietary flavonoids (25).

One feature of this study was the lower variability, as evaluated from the standard deviation of the inhibitory effects, of levocetirizine compared with fexofenadine. This confirms the wheal and flare study of Grant and colleagues (6) in which the authors commented that the inter-subject variability was lower for levocetirizine com-

pared with the other antihistamine treatments, including fexofenadine 180 mg. It is noteworthy that the inhibition of wheal diameter, wheal volume and flare diameter were all correlated with the AUC (0–12 h) of the fexofenadine plasma concentrations, suggesting that the variability of blood levels of this drug made a significant contribution to its differing efficacy between individuals. No such correlation was found for levocetirizine.

The inhibitory effects of levocetirizine confirm previous publications in its rapid onset of action (within 1 hour), time of maximum effect (3–4 h), mean efficacy (70–90%) and duration of action (at least 24 h) (6, 12, 26, 27). The greater consistency of effect of levocetirizine was illustrated by the number of volunteers showing a greater than 75% inhibition of wheal and flare responses. This is consistent with the study of Grant and colleagues (6). This is also consistent with a meta-analysis of several allergen challenge chamber studies and allergic rhinitis clinical trials (28) in which levocetirizine was shown to exhibit consistent and significant efficacy on nasal and ocular symptoms regardless of the subjects' gender, age, baseline symptom severity scores, pollen exposure conditions, or medical history. The somewhat slower onset of action (around 2 h), time of maximum effect (3–6 h), mean efficacy (50–80%) and shorter duration of action (around 12 h), of 60 mg fexofenadine are consistent with the wheal and flare study of Boyle and colleagues (11).

That the duration of action of both levocetirizine and fexofenadine is not dependent on their plasma concentrations can be seen clearly from the hysteresis loops for inhibition of the flare response. As explained in the review by Church & Maurer (5), $H_1$-antihistamines need to diffuse from the circulation into the extravascular spaces before they can exert their inhibitory effects. Because both levocetirizine and fexofenadine exist as zwitterions (29, 30), i.e. neutral molecules with a positive and a negative electrical charge at different locations within their structure, they are always ionised and cross biological membranes poorly. From the hysteresis loops, it is clear that both drugs require up to 4 h to accumulate in the extravascular space where they become 'trapped' so prolonging their duration of action even though their plasma concentrations fall to very low levels.

One further important consideration in this study was the possibility of differences between Caucasian and Japanese men. Analysis of the pruritus data following placebo administration showed the Japanese men to have significantly ($p = 0.031$) higher VAS scores than their Caucasian counterparts. Whether this represents a higher than normal responsiveness of the Japanese group to histamine or a lower than normal responsiveness of the Caucasian group is not known. When considering the responsiveness to the study drugs, other than a marginally greater responsiveness of the Japanese individuals to fexofenadine, there were no significant differences between the groups. This confirms the conclusions of previous studies that there are no ethnic differences in the responsiveness of individuals to $H_1$-antihistamines (9, 31).

In conclusion, in this study in healthy volunteers, levocetirizine had a highly significantly greater ($p < 0.005$) inhibitory effect than fexofenadine on the pruritic response, the wheal response measured both as diameter and volume and the flare response. Furthermore, levocetirizine had a more rapid onset of action, a shorter time to maximum effect and a longer duration of action than fexofenadine. Also, the number of individuals with a $>75\%$ reduction of response was higher with levocetirizine than fexofenadine showing a greater consistency of action for levocetirizine. There were no clinically significant ethnic differences in the responsiveness to the drugs.

## ACKNOWLEDGEMENTS

We are indebted to Annika Ostermann (Berliner Betrieb für Zentrale Gesundheitliche Aufgaben, Institut für Toxikologie, Klinische Toxikologie und Giftnotruf Berlin, Fachbereich Klinische Toxikologie und Pharmakologie) for measurement of plasma levels of levocetirizine and fexofenadine. The study was supported by an unrestricted grant from GlaxoSmithKline K.K.,Tokyo, Japan.

*Conflicts of interest:* Martin Church has been a speaker or consultant for Almirall, FAES Pharma, Menarini, MSD, UCB Pharma, Sanofi-Aventis, and Uriach. Marcus Maurer has been a speaker or consultant for Almirall, FAES Pharma, Genentech, Menarini, MSD, Novartis, UCB Pharma, Sanofi-Aventis, and Uriach. Nicole Schoepke declares no conflict of interest.

## REFERENCES

1. Kapp A, Pichler WJ. Levocetirizine is an effective treatment in patients suffering from chronic idiopathic urticaria: a randomized, double-blind, placebo-controlled, parallel, multicenter study. Int J Dermatol 2006; 45: 469–474.
2. Staevska M, Popov TA, Kralimarkova T, Lazarova C, Kraeva S, Popova D, et al. The effectiveness of levocetirizine and desloratadine in up to 4 times conventional doses in difficult-to-treat urticaria. J Allergy Clin Immunol 2010; 125: 676–682.
3. Finn AF, Jr., Kaplan AP, Fretwell R, Qu R, Long J. A double-blind, placebo-controlled trial of fexofenadine HCl in the treatment of chronic idiopathic urticaria. J Allergy Clin Immunol 1999; 104: 1071–1078.
4. Markham A, Wagstaff AJ. Fexofenadine. Drugs 1998; 55: 269–274.
5. Church MK, Maurer M. H1-antihistamines and urticaria: how can we predict the best drug for our patient? Clin Exp Allergy 2012; 42: 1423–1429.
6. Grant JA, Riethuisen JM, Moulaert B, DeVos C. A double-blind, randomized, single-dose, crossover comparison of levocetirizine with ebastine, fexofenadine, loratadine, mizolastine, and placebo: suppression of histamine-induced wheal-and-flare response during 24 hours in healthy male subjects. Ann Allergy Asthma Immunol 2002; 88: 190–197.
7. Kruszewski J, Klos K, Sulek K. [Inhibition of histamine-induced wheel after a recommended single dose administra-

tion of 10 mg cetirizine, 5 mg desloratadine, 120 and 180 mg fexofenadine, 5 mg levocetirizine and 10 mg loratadine – a randomized, double-blind, placebo controlled trial]. Pol Merkur Lekarski 2006; 21: 443–448 (in Polish).
8. Dhanya NB, Thasleem Z, Rai R, Srinivas CR. Comparative efficacy of levocetirizine, desloratidine and fexofenadine by histamine wheal suppression test. Indian J Dermatol Venereol Leprol 2008; 74: 361–363.
9. Kawashima M, Harada S, Tango T. Review of fexofenadine in the treatment of chronic idiopathic urticaria. Int J Dermatol 2002; 41: 701–706.
10. Nelson HS, Reynolds R, Mason J. Fexofenadine HCl is safe and effective for treatment of chronic idiopathic urticaria. Ann Allergy Asthma Immunol 2000; 84: 517–522.
11. Boyle J, Ridout F, Meadows R, Johnsen S, Hindmarch I. Suppression of the histamine-induced wheal and flare response by fexofenadine HCl 60 mg twice daily, loratadine 10 mg once daily and placebo in healthy Japanese volunteers. Curr Med Res Opin 2005; 21: 1495–1503.
12. Purohit A, Melac M, Pauli G, Frossard N. Twenty-four-hour activity and consistency of activity of levocetirizine and desloratadine in the skin. Br J Clin Pharmacol 2003; 56: 388–394.
13. Glaeser H, Bailey DG, Dresser GK, Gregor JC, Schwarz UI, McGrath JS, et al. Intestinal drug transporter expression and the impact of grapefruit juice in humans. Clin Pharmacol Ther 2007; 81: 362–370.
14. Simons KJ, Strolin Benedetti M, Simons FE, Gillard M, Baltes E. Relevance of H1-receptor occupancy to H1-antihistamine dosing in children. J Allergy Clin Immunol 2007; 119: 1551–1554.
15. Strolin Benedetti M, Plisnier M, Kaise J, Maier L, Baltes E, Arendt C, et al. Absorption, distribution, metabolism and excretion of (14C)levocetirizine, the R enantiomer of cetirizine, in healthy volunteers. Eur J Clin Pharmacol 2001; 57: 571–582.
16. Molimard M, Diquet B, Strolin Benedetti M. Comparison of pharmacokinetics and metabolism of desloratadine, fexofenadine, levocetirizine and mizolastine in humans. Fundam Clin Pharmacol 2004; 18: 399–411.
17. Strolin Benedetti M, Whomsley R, Mathy FX, Jacques P, Espie P, Canning M. Stereoselective renal tubular secretion of levocetirizine and dextrocetirizine, the two enantiomers of the H1-antihistamine cetirizine. Fundam Clin Pharmacol 2008; 22: 19–23.
18. Baltes E, Coupez R, Giezek H, Voss G, Meyerhoff C, Strolin Benedetti M. Absorption and disposition of levocetirizine, the eutomer of cetirizine, administered alone or as cetirizine to healthy volunteers. Fundam Clin Pharmacol 2001; 15: 269–277.
19. Crowe A, Wright C. The impact of P-glycoprotein mediated efflux on absorption of 11 sedating and less-sedating antihistamines using Caco-2 monolayers. Xenobiotica; 2012; 42: 538–549.
20. Cvetkovic M, Leake B, Fromm MF, Wilkinson GR, Kim RB. OATP and P-glycoprotein transporters mediate the cellular uptake and excretion of fexofenadine. Drug Metab Dispos 1999; 27: 866–871.
21. Kalliokoski A, Niemi M. Impact of OATP transporters on pharmacokinetics. Br J Pharmacol 2009; 158: 693–705.
22. Rebello S, Zhao S, Hariry S, Dahlke M, Alexander N, Vapurcuyan A, et al. Intestinal OATP1A2 inhibition as a potential mechanism for the effect of grapefruit juice on aliskiren pharmacokinetics in healthy subjects. Eur J Clin Pharmacol 2012; 68: 697–708.
23. Bailey DG. Fruit juice inhibition of uptake transport: a new type of food-drug interaction. Br J Clin Pharmacol 2010; 70: 645–655.
24. Matsushima S, Maeda K, Hayashi H, Debori Y, Schinkel AH, Schuetz JD, et al. Involvement of multiple efflux transporters in hepatic disposition of fexofenadine. Mol Pharmacol 2008; 73: 1474–1483.
25. Taur JS, Rodriguez-Proteau R. Effects of dietary flavonoids on the transport of cimetidine via P-glycoprotein and cationic transporters in Caco-2 and LLC-PK1 cell models. Xenobiotica London 2008; 38: 1536–1550.
26. Denham KJ, Boutsiouki P, Clough GF, Church MK. Comparison of the effects of desloratadine and levocetirizine on histamine-induced wheal, flare and itch in human skin. Inflamm Res 2003; 52: 424–427.
27. Passalacqua G, Guerra L, Compalati E, Massacane P, Rogkakou A, Zanella C, et al. Comparison of the effects in the nose and skin of a single dose of desloratadine and levocetirizine over 24 hours. Int Arch Allergy Immunol 2004; 135: 143–147.
28. Boev R, Song D, Bedenbaugh A, Haeusler JM. Improving SAR symptoms with levocetirizine: evaluating active and placebo effects in pollen challenge vs. natural exposure studies. Curr Med Res Opin 2011; 27: 107–114.
29. Chen C. Physicochemical, pharmacological and pharmacokinetic properties of the zwitterionic antihistamines cetirizine and levocetirizine. Curr Med Chem 2008; 15: 2173–2191.
30. Tessler L, Goldberg I. The methanol disolvate and the dihydrate of fexofenadine, an antihistamine drug. Acta Crystallogr C 2005; 61: o707–o710.
31. Boyle J, Eriksson M, Stanley N, Fujita T, Kumagi Y. Allergy medication in Japanese volunteers: treatment effect of single doses on nocturnal sleep architecture and next day residual effects. Curr Med Res Opin 2006; 22: 1343–1351.