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Original article

A randomized, double-blind, crossover comparison among cetirizine, levocetirizine, and ucb 28557 on histamine-induced cutaneous responses in healthy adult volunteers

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Background: Cetirizine is a highly efficacious and long-acting second-generation H_1-receptor antagonist for the treatment of allergic diseases, such as allergic rhinitis and chronic idiopathic urticaria, in adults and children. Pharmacologic studies have demonstrated that cetirizine, a racemate mixture composed of equal amounts of two enantiomers, does not undergo hepatic metabolism to any significant level. The enantiomers are excreted mainly unchanged, predominantly in the urine and to a lesser extent in the faeces.

Methods: The pharmacologic activity and potency of the two enantiomers of cetirizine in the management of allergic skin conditions were investigated by studying the effect of treatment with 5.0 mg cetirizine; 2.5 mg levocetirizine, the (*R*)-enantiomer; and 2.5 mg ucb 28557, the (*S*)-enantiomer, on histamine-induced wheal and flare response in 18 healthy volunteers. Each treatment was administered as a single oral dose in randomized, double-blind, and crossover manner, and the efficacy of treatment was assessed over a period of 32 h, as per cent inhibition of the histamine-induced wheal and flare areas before treatment. Blood and urine samples were collected in a time-dependent manner and analyzed for the total amounts of each study drug, to elucidate their pharmacokinetic profiles.

Results: Both cetirizine and levocetirizine caused a marked inhibition of histamine-induced wheal and flare, whereas ucb 28557 was inactive in this model. Inhibition of the wheal response observed for cetirizine and levocetirizine was apparent by 1 h after dosage and lasted for mean durations of 24.4 and 28.4 h, respectively. In addition, the response for cetirizine and levocetirizine became maximal by 6 h after treatment, rising to 79.5% and 83.8%. Similarly, cetirizine and levocetirizine also markedly inhibited the histamine-induced flare response. This effect was evident for both drugs by 1 h after dosage and lasted over a mean period of 28.4 and 26.0 h, respectively, for cetirizine and levocetirizine. The inhibitory effect of these compounds on histamine-induced flare response was also maximal by approximately 6 h after dosage, peaking at 88.5% and 83.6%, respectively. Statistical evaluation showed that cetirizine and levocetirizine were equivalent for maximum inhibition of histamine-induced wheal and flare. However, levocetirizine was found to be superior to cetirizine when area under the curve was compared. In contrast, ucb 28557 was not found to inhibit histamine-induced wheal and flare responses at any time during the study period. Plasma concentrations of levocetirizine were found to be approximately double those of ucb 28557 at 4 and 8 h after dosing, and 50–60% of the drugs were excreted unchanged in urine over a period of 32 h.

Conclusions: The finding that, in this model, levocetirizine 2.5 mg has comparable antihistaminic activity to cetirizine 5 mg, whereas its other enantiomer ucb 28557 has no pharmacodynamic effect, suggests that the antihistaminic properties of cetirizine observed in the management of allergic skin conditions are likely to be attributable to levocetirizine.

Key words: antihistamines; cetirizine; equivalence; levocetirizine; ucb 28557; urinary excretion; urticaria.

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Several studies have suggested that histamine plays a central role in the pathologic effects of urticaria (1, 2). Comparative studies of patients with chronic urticaria and healthy subjects have demonstrated that the urticaria patients release greater amounts of histamine than the healthy subjects, both sponta-

neously and after antigen provocation (3–5). Similarly, some studies have demonstrated that the responsiveness of the skin to histamine is slightly increased in patients with urticaria (3).

In the skin, histamine is stored primarily in the mast cells and on release leads to parasympathetic nerve stimulation and increased vascular permeability (6, 7), resulting in the formation of itchy, slowly expanding, erythematous wheals (3). Mechanistic studies have demonstrated that the effects of histamine arise from its interaction with one or more of three histamine receptors, H_1, H_2, and H_3 (8–10), of which activation of the H_1 receptors is thought to be the most important in urticaria, in view of the prominent and highly efficacious use of H_1 receptor antagonists in the treatment of this condition (11–13).

Studies of cetirizine have demonstrated that this compound has a greater selectivity for the H_1-receptors and low hepatic metabolism, in contrast to many other second-generation antihistamines (14, 15). Several double-blind, crossover, or parallel-group studies have demonstrated that cetirizine is significantly superior to placebo and some of the other H_1-receptor antagonists in providing general symptomatic relief from pruritis, wheals, and flares in chronic idiopathic urticaria and some physical urticarias (14). Similarly, several double-blind, crossover studies in healthy volunteers have also demonstrated that cetirizine is more effective than either placebo or most of the other H_1-receptor antagonists in attenuating the wheal and flare response resulting from epicutaneous or intradermal administration of histamine in these individuals (14, 16). Numerous pharmacodynamic studies have also demonstrated that a single intake of 10 mg cetirizine, the normal daily therapeutic dose, is highly potent and prevents the formation of wheals and flares for several hours after dosage.

Chemical analysis of cetirizine has demonstrated that it is a racemate preparation composed of equal quantities of the levocetirizine and ucb 28557 enantiomers, but, to date, there is no information on the efficacy of either enantiomer in the treatment of urticaria. Consequently, the aim of this study was to compare the effect of the racemic mixture with the two enantiomers of cetirizine on histamine-induced skin wheal and flare reaction in healthy volunteers. However, since a therapeutic dosage of 10 mg cetirizine has been shown to inhibit completely up to 100 mg/ml histamine-induced skin wheal and flare reactions in human volunteers, at 2–12 h after administration, it was essential that a dose lower than 10 mg cetirizine be investigated in order to observe any equivalence of pharmacodynamic action between cetirizine and one of its enantiomers. Consequently, since this was an equivalence study design, the effects of a single oral dose of 5 mg cetirizine (the ED_{50} of the recommended 10-mg therapeutic dose necessary for such a study design) and 2.5-mg oral doses of each enantiomer were investigated.

Material and methods

Subjects

Nineteen healthy white male volunteers entered the study, of whom one withdrew after the first treatment for personal reasons. The 18 volunteers who completed the study were of average frame, with a mean age of 26.4 years (range 18–41 years), and all demonstrated a histamine-induced mean skin wheal diameter of $\geq$8 mm by skin prick test with 100 mg/ml histamine solution. None of the volunteers, however, was skin prick test positive to any of the common allergens, including house-dust mite, animal dander, and grass and tree pollen. Similarly, none of the volunteers demonstrated any reaction to skin puncture without the histamine solution (negative control). On entry, none of the volunteers showed any sign of illness, as indicated by medical history and examination; they had normal ECG, and clinically acceptable serum/urine biochemistry, haematology, and serology; and none were taking any prescribed or investigation medication during the 2–4 weeks preceding enrolment. All volunteers' backs were also checked to ensure the absence of skin blemishes such as acne, tattoos, and hair, the presence of any one of which constituted a study-exclusion criterion.

Eleven of the volunteers were smokers, and 17 volunteers consumed alcohol in moderation. All volunteers gave written informed consent before entry into the study, which was approved by the Independent Review Board of the Besselaar Clinical Research Unit, Leeds, UK.

Study design

This was a double-blind, three-treatment, crossover study. After the screening visit, each eligible volunteer was entered into a randomization schedule to receive 2.5 mg levocetirizine, 2.5 mg ucb 28557, and 5.0 mg cetirizine, and was investigated as a member of series groups of nine volunteers, each dosed on three separate occasions. Each group of individuals attended the clinic in the evening of the day before the dosing day, and each volunteer was subjected to a urine drug screen, including alcohol and cannabinoids. The volunteer was provided with a meal and accommodation for overnight stays, and was scheduled for dosing and testing the following day.

A baseline skin prick test was performed on the volunteer's back with 100 mg/ml histamine solution before dosing, and then again at several time points from 1 to 32 h after dosing. The test was performed at a different site each time, and the area of the skin wheal and flare was measured after each test. A negative skin prick test (puncture without the histamine solution) was not performed, since none of the volunteers had demonstrated any reaction during screening. Blood samples of 5 ml were taken by venepuncture of a forearm vein before dosing, and at 4 and 8 h after dosing, for analysis of the study drugs.

Similarly, urine samples were also collected for analysis of the study drugs at 0–1 h before dosing, and then at any time during time spans of 0–4, 4–8, 8–12, 12–24, and 24–32 h after dosing.

The volunteers returned to the clinic on two further occasions after intervals of 7 days, and the experimental procedure was repeated before dosing with the second and the third treatment. A set menu of breakfast, lunch, evening meal, and a light snack was served to each volunteer at 2, 5, 10, and 13 h, respectively, after dosing, during each study period.

Skin prick test

Skin prick tests were performed on the upper half of volunteers' backs before dosing and at 1, 2, 3, 4, 5, 6, 8, 12, 24, and 32 h after dosing. A droplet of 100 mg/ml histamine solution was placed on an untested site and administered into the skin by piercing the superficial skin with a sterile lancet. The droplet was gently wiped off after 1 min, and the wheal and flare reaction was visualized under a bright lamp after 15 min. The size of the wheal and flare was outlined with thin-tipped marker pens and then traced onto an acetate sheet to make a permanent record, which was used later for analysis of areas of the wheal and flare. The area of the wheal and flare was measured by computerized planimetry, by a person blinded to the study protocol, and expressed as square millimetres.

Measurement of cetirizine, levocetirizine, and ucb 28557 in blood and urine samples

Blood samples were collected into 5-ml lithium heparin vacutainer tubes (Becton-Dickinson Ltd, Oxford, UK) and centrifuged at 1500 *g* for 10 min at 0–5°C. The plasma was aspirated carefully and stored in polypropylene tubes at −20°C before analysis by achiral HPLC. Urine samples were collected in preweighed polypropylene containers; after the weight of each sample was recorded, 20-ml samples were stored in duplicate in polypropylene tubes at −20°C until analysis by both chiral and achiral HPLC.

Determination of levocetirizine, ucb 28557, and cetirizine in plasma samples (achiral procedure). Volumes of 100 µl of 10 µg/ml ucb 26255 (the internal standard) and 1 ml of 1 mol/l citrate-phosphate buffer, pH 5.1, were added to 1-ml aliquots of plasma samples, diluted, if necessary, by blank plasma. Levocetirizine, ucb 28557, cetirizine, and the internal standard present in the samples were extracted twice with 3 ml ethyl acetate, and phosphoric acid (1.7% v/v, 0.5 ml) was added to the pooled organic extracts. After thorough mixing, the mixture was centrifuged at 3000 *g* for 5 min to separate the acidic and the organic phases. The organic phase was discarded, and a gentle stream of dry, oxygen-free nitrogen was passed over the acidic extracts for a few minutes to remove any residual ethyl acetate. The acidic extract was then transferred into vials for autosamplers before analysis by HPLC, with a Hewlett-Packard 1090B liquid chromatograph equipped with a variable wavelength detector. A volume of 150 µl of each sample was injected onto a 220 × 4.6 mm (internal diameter) 5-µm Brownlee Spheri-5 column, equipped with a MOS-hypersil (20 × 4 mm, 5 µm) guard column, and chromatography was performed with a mobile phase composed of KH_2PO_4 (0.01 mol/l)/acetonitrile (45/55 v/v) containing sodium octane sulphonate (0.02 mol/l), and adjusted to pH 3. The flow was adjusted to 1.5 ml/min, and the column was maintained at 50°C during chromatography. Levocetirizine, ucb 28557, or cetirizine present in the samples was detected at 230 nm, and estimated from a calibration curve prepared from blank plasma samples spiked with known amounts of the two compounds in a nominal range of 10–750 ng/ml.

Determination of levocetirizine, ucb 28557, or cetirizine in urine samples (achiral procedure). Aliquots (1 ml) of urine samples, diluted if necessary, were transferred to 20-ml glass extraction tubes, and mixed with 100 µl of the internal standard (ucb 26255, 30 µg/ml), citrate buffer (1 mol/l, pH 5, 1 ml), and chloroform (10 ml), in a shaker for 10 min. After mixing, the samples were centrifuged at 3000 *g* for 10 min. The organic layer was transferred to a clean tube and evaporated to dryness under a gentle stream of dry, oxygen-free nitrogen at 50°C. The dry extracts were then reconstituted with 100-µl aliquots of mobile phase and transferred into vials for autosamplers, before analysis by HPLC, with a Hewlett-Packard 1090M liquid chromatograph (series II) equipped with an HP 1050 variable wavelength detector. A volume of 30 µl of each sample was injected onto a 200 × 4.3 mm (internal diameter) 5-µm ODS column, and chromatography was performed with a mobile phase composed of H_2O/methanol (35/65 v/v) containing tetrabutyl ammonium (Pic A low UV, 0.005 mol/l), at a flow rate of 1.5 ml/min. The column was maintained at a temperature of 50°C and the detector set at 235 nm during chromatography. The amounts of levocetirizine, ucb 28557, or cetirizine present in the samples were estimated from a calibration curve prepared from blank plasma samples spiked with known amounts of the two compounds in a nominal range of 0.05 to 6 µg/ml.

Determination of levocetirizine and ucb 28557 in urine samples collected after cetirizine dosing (chiral procedure). Before analysis, a 1.0-ml aliquot of each sample was mixed with 1.0 ml of 1 mol/l citrate buffer, pH 5.0, and 3.0 ml ethyl acetate for 10 min, and then centrifuged at 3000 *g* for 10 min. The upper organic layer was transferred to a clean tube, and the aqueous phase was extracted again with 3 ml ethyl acetate. After centrifugation, the two ethyl acetate phases were combined and mixed with 0.5 ml H_3PO_4 (1.7% v/v), for 10 min as above. The aqueous phase derived from this mixture was evaporated to dryness under a gentle stream of nitrogen, and the sample was reconstituted in 100 µl of the HPLC mobile phase before analysis by HPLC. Calibration and quality control samples were spiked with a known amount of cetirizine dihydrochloride, and also processed as above.

Samples were analysed with a Hewlett-Packard 1090 DR5 liquid chromatograph equipped with a HP 1050 variable wavelength detector. A volume of 50 µl of each sample was injected onto a 250 mm × 4 mm (internal diameter) 5-µm Chiracel OD-H column (Daicel Chemical Industries Ltd, Tokyo, Japan), equipped with a 10-µm Chiralcel OD 50 × 4 mm guard column, and chromatography was performed with a mobile phase composed of H_2O:CH_3CN (72.5:27.5, v/v). The aqueous fraction of the mobile phase contained 0.01 mol/l KH_2PO_4 and 0.02 mol/l sodium octane sulphonate, and was adjusted to pH 2 with H_3PO_4 before use. The flow was adjusted to 0.6 ml/min, the oven temperature was maintained at 40°C, and the detector was set at 230 nm during chromatography. The amounts of levocetirizine and ucb 28557 present in the samples were estimated from a calibration curve prepared from blank urine samples spiked with known amounts of the two compounds in nominal ratios of 70/30, 60/40, 50/50, 40/60, and 30/70.

Statistical analysis

Per cent inhibition of the histamine-induced effect, after treatment with the study drug, was calculated from the absolute values of areas estimated for histamine-induced wheal and flare at baseline (before treatment) and at each time point after treatment, according to the following formula:

$$I_t = \frac{(S_0 - S_t)}{S_0} \times 100$$

where S_0 and S_t are wheal/flare areas at time 0 (baseline) and at time *t*, respectively.

The results for areas and per cent inhibition of histamine-induced wheal/flare for all individuals were expressed as mean (±SEM) values for each time point, and plotted as time-response curves for wheal and flare and per cent inhibition of these responses. Each curve for the wheal/flare response at 0–32 h and

the per cent inhibition of these responses after treatment was analysed for area under the curve ($AUC_{0–32}$ and $AUC\text{-}inh_{0–32}$, respectively), by the linear trapezoidal rule. The time curves demonstrating inhibitory effects of the study drugs were also evaluated for the time of maximum inhibition (t_{max}) and the duration of the inhibitory effect observed with each drug. The latter was determined by noting the time from when an inhibition of $\geq 20\%$ over baseline was first observed (t_{onset}), to the time when inhibition reverted to $<20\%$ over baseline (t_{end}). The significance of any differences between the curves for any two treatments was tested by ANOVA for a two-period crossover design, and the significance of any differences in t_{max}, t_{onset}, and t_{end} and the duration of inhibition was analysed by Wilcoxon's rank sum test on the treatment effect. Equivalence tests were also performed for histamine-induced wheals and flares for $AUC_{0–32}$, $AUC\text{-}inh_{0–32}$, and maximum inhibition, by the two one-sided tests of Schuirmann (17, 18). These tests used a significance level of 0.05. The equivalence was accepted if the 90% confidence interval of the ratio of means was fully included in the range 0.8–1.20.

The results for the amounts of each drug excreted in the urine over a period of 0–32 h were expressed as cumulative amounts and tested for significance of differences by ANOVA for a two-period crossover design.

Results

Effect of treatment with cetirizine, levocetirizine, and ucb 28557 on histamine-induced wheal and flare

The mean areas of histamine-induced wheal and flare are shown in Figs. 1 and 2, respectively. The baseline wheal and flare areas were not found to be significantly different before treatment with any of the three study drugs. Treatment with oral cetirizine (5 mg) and oral levocetirizine (2.5 mg) progressively decreased the size of the wheals and flares induced by histamine as the time after treatment was increased from 0 to 32 h. In contrast, treatment with oral ucb 28557 (2.5 mg) did not alter the size of histamine-induced wheals and flares over this period.

Estimation of the per cent inhibition of the histamine-induced wheal and flare response confirmed that cetirizine and levocetirizine, but not ucb 28557, were active in this respect. The inhibition profiles of histamine-induced wheal for cetirizine and levocetirizine demonstrated that they were comparable (Fig. 3). Inhibition of the wheal by cetirizine and levocetirizine was apparent and pronounced (22.5% and 30.2%, respectively) by 1 h after dosage, and maximal (79.5% and 83.8%, respectively) at approximately 6 h after dosage. Although the mean onset time for inhibition for both compounds was found to be 1.6 h after dosage, and both compounds were effective over the entire period of 32 h investigated, levocetirizine caused a greater wheal inhibition of 40.2% at 32 h after dosage, compared with the 24.3% inhibition caused by cetirizine. Similarly, the mean duration of the inhibitory response was found to be slightly prolonged at 28.4 h for levocetirizine, compared with 24.3 h for cetirizine.

Analysis of the inhibitory profiles for histamine-induced flare demonstrated that these were also comparable for cetirizine and levocetirizine (Fig. 4). Cetirizine and levocetirizine, respectively, inhibited this response by 13.4% and 10.2% by 1 h after dosage, and maximally by 88.5% and 83.6% by approximately 6 h after dosage. Inhibition of the flare was also apparent over the entire 32-h study period, but in contrast to the effect on wheal, the effect on flare was found to be greater at 36.1% for cetirizine than the 24.5% inhibition observed for levocetirizine at 32 h after dosage. Although the mean onset time for inhibition of the flare for cetirizine and levocetirizine were comparable at 1.9 and 2.0 h, respectively, the mean duration of the inhibitory response for cetirizine was found to slightly prolonged at 28.4 h, compared with 26.0 h for levocetirizine.

However, statistical analysis of the inhibitory profiles of cetirizine and levocetirizine demonstrated that with the exception of $AUC\text{-}inh_{0–32}$, for wheal, there were no significant differences in percentage of maximum inhibition, time of maximum inhibition (t_{max}), onset time (t_{onset}), end time (t_{end}) and duration of inhibition of the wheal or flare for the two compounds (Table 1).

The assessment of equivalence between cetirizine and levocetirizine (as indicated by 90% confidence interval fully contained in the range of 0.8–1.20 of the ratio of means) demonstrated these compounds to be similar in potency with respect to the maximum inhibition they achieved on histamine-induced wheal and flare. However, assessment of equivalence in $AUC\text{-}inh_{0–32}$ and $AUC_{0–32}$ between cetirizine and levocetirizine was not established for either wheal or flare (larger 90% CI in flare). A greater inhibitory effect on histamine-induced wheal ($AUC\ inh_{0–32}$) was observed for levocetirizine than for cetirizine (super-equivalence for wheal area, as the ratio levocetirizine/cetirizine was 1.47, with 90% CI [1.16–1.79]). This was related to the longer pharmacodynamic effect of levocetirizine than cetirizine (Table 2).

Determination of cetirizine, levocetirizine, and ucb 28557 in plasma and urine

The retention times for levocetirizine and ucb 28557, under the chromatographic conditions used, were 38 and 34 min, respectively. Adjusted recovery from spiked plasma and urine control samples was found to be 90–100% for each enantiomer. The technique was highly reproducible, as indicated by the within-study variability of 10.5% and 6.9% for plasma and urine samples, respectively. Similarly, achiral analysis demonstrated that 95–101% of levocetirizine, and 97–102% of ucb 28557 were recovered from spiked urine samples.

Analysis of plasma samples from all volunteers demonstrated that each study drug was detectable in

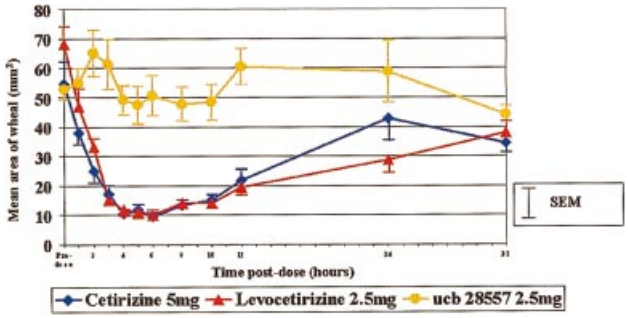

Figure 1. Effect of treatment with single oral dose of 5.0 mg cetirizine, 2.5 mg levocetirizine, and 2.5 mg ucb 28557 on mean area of wheal induced by histamine over period of 32 h.

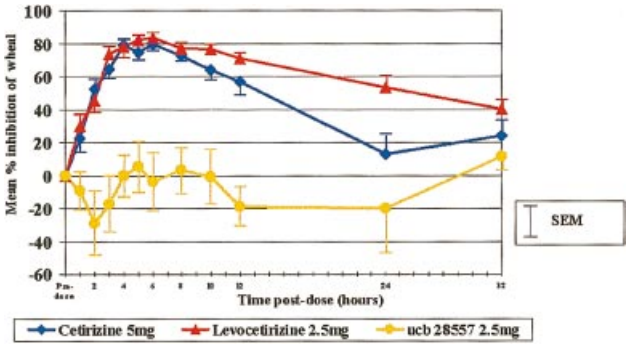

Figure 3. Mean per cent inhibition of histamine-induced wheal after treatment with single oral dose of 5.0 mg cetirizine, 2.5 mg levocetirizine, and 2.5 mg ucb 28557 over period of 32 h.

these samples at 4 and 8 h after dosage, thereby confirming the compliance with treatment randomization and dosing schedules. Indeed, plasma concentrations of cetirizine were similar to the summed plasma concentrations of the two enantiomers given separately. However, analysis of the plasma concentrations (mean $\pm$ SEM) of levocetirizine at 4 h after dosage (77.9 $\pm$ 3.6 ng/ml) and 8 h after dosage (53.1 $\pm$ 2.9 ng/ml) showed that these were higher than plasma concentrations of ucb 28557 at 4 h after dosage (41.2 $\pm$ 3.6 ng/ml) and 8 h after dosage (24.2 $\pm$ 3.8 ng/ml).

The mean cumulative excretion of levocetirizine and ucb 28557, as determined by chiral analysis after administration of cetirizine, was progressively increased to 60.8% and 50.9% of the dose, respectively, at 32 h after dosage. Statistical analysis demonstrated that the mean cumulative excretion of levocetirizine was significantly greater than the mean cumulative excretion of ucb 28557 ($P < 0.02$).

The mean cumulative excretion of levocetirizine, when given as the single enantiomer, progressively increased to 57.8% by 32 h after dosage, and was not significantly different from that when given as the racemate. Similarly, the mean cumulative excretion of ucb 28557, when given as a single enantiomer, progressively increased to 50.4% by 32 h after dosage, and was also not significantly different from that when given as the racemate.

Evaluation of safety

None of the 18 volunteers investigated experienced any serious adverse events, and all tolerated the study drugs well. Although a total of nine adverse events were recorded during the study, there was no clearly drug-related trend in the distribution of adverse events. Five of these adverse events, including headache, blocked nose, blocked sinuses, dry cough, and urticaria in the lower back were observed in four individuals after treatment with cetirizine. One individual experienced headache after treatment with levocetirizine, and two individuals experienced headache and/or urticaria in the buttocks or arm/back after treatment with ucb 28557.

Discussion

Our study has demonstrated that treatment with

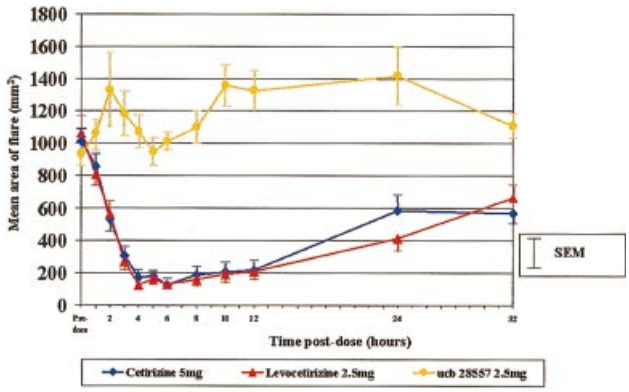

Figure 2. Effect of treatment with single oral dose of 5.0 mg cetirizine, 2.5 mg levocetirizine, and 2.5 mg ucb 28557 on mean area of flare induced by histamine over period of 32 h.

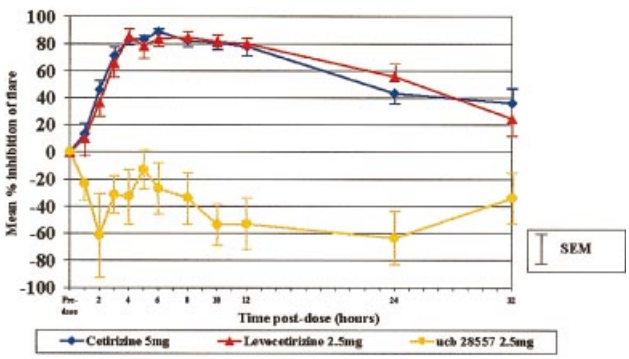

Figure 4. Mean per cent inhibition of histamine-induced flare after treatment with single oral dose of 5.0 mg cetirizine, 2.5 mg levocetirizine, and 2.5 mg ucb 28557 over period of 32 h.

Table 1. Statistical analysis of inhibition profiles of cetirizine and levocetirizine

Parameters (unit)		Treatment: Cetirizine ($n=18$)	Treatment: Levocetirizine ($n=18$)	P value
AUC-Inh$_{0-32\ h}$ [1]	Wheal	1314 ± 222	1938 ± 113	0.018
(%.h)	Flare	1877 ± 165	1946 ± 188	0.74
A_{max} [1]	Wheal	89 ± 2	92 ± 2	0.056
(%)	Flare	94 ± 1	95 ± 1	0.42
AUC$_{0-32\ h}$ [1]	Wheal	917 ± 118	797 ± 75	0.22
(mm^2.h)	Flare	13202 ± 1690	11665 ± 1512	0.75
t_{max} [2]	Wheal	5.5 (3–12)	5.0 (3–12)	0.86
(h)	Flare	6.0 (3–10)	6.0 (4–12)	0.62
t_{onset} [2]	Wheal	1.0 (1–3)	1.0 (1–5)	0.73
(h)	Flare	2.0 (1–4)	1.0 (1–8)	0.71
t_{end} [2]	Wheal	32.0 (10–32)	32.0 (12–32)	0.21
(h)	Flare	32.0 (10–32)	32.0 (12–32)	0.29
Duration [2]	Wheal	30.5 (8–31)	31.0 (11–31)	0.13
(h)	Flare	30.0 (6–31)	30.0 (4–31)	0.72

[1]Arithmetic mean (± SEM).
[2]Median (range).

2.5 mg levocetirizine causes a marked inhibition of histamine-induced wheal and flare response in healthy volunteers, an inhibition that is comparable to the effect of 5 mg cetirizine. Both drugs appeared to be comparable in activity in that inhibition is apparent from the first assessment at 1 h after dosage to the last assessment at 32 h after dosage, and maximal inhibition of 90–95% occurred at approximately 6 h after dosage. Comparison of pharmacodynamic effects has demonstrated equivalence for the two compounds with respect to the maximum level of inhibition that can be achieved. In addition, our study has demonstrated that the degree and time course of histamine-induced wheal and flare inhibition are similar when levocetirizine is administered either alone, as the single enantiomer, or as a racemic mixture cetirizine. In contrast to treatment with cetirizine and levocetirizine, treatment with ucb 28557 does not show any relevant or consistent inhibition of the histamine-induced wheal and flare in these individuals.

This is the first study to compare and contrast the effect of treatment with cetirizine and its enantiomers on the skin wheal and flare response induced by histamine or any other compound eliciting this effect in human subjects. In view of the similarity of the antihistaminic effects observed for cetirizine and levocetirizine, and the lack of any effect for ucb 28557 in this pharmacologic model, these data suggest that the antihistaminic effects demonstrated thus far for cetirizine in the management of allergic skin conditions are likely to be due to levocetirizine. Indeed, our findings indicate higher plasma concentrations for levocetirizine than ucb 28557 at either 4 or 8 h after dosage. These data also indicate a higher urinary excretion ratio for levocetirizine than for ucb 28557. Moreover, the observation that treatment with levocetirizine was generally well tolerated in these healthy volunteers also suggests that this compound is likely to be safe.

Our results for cetirizine are in accordance with the findings of others. Grant et al. (19) have recently performed a double-blind, randomized, placebo-controlled, crossover study to compare the inhibition profiles of various second-generation H_1-antihistamines, including cetirizine, ebastine, epinastine, fexofenadine, terfenadine, and loratadine, on the histamine-induced cutaneous response in 14 healthy male volunteers. All volunteers were treated with a single recommended therapeutic oral dose of each antihistamine, with a 1-week washout period between each treatment, and after treatment, they underwent the histamine skin prick test several times over a period of 0–24 h. These authors demonstrated that inhibition of the histamine-induced wheal and flare response by 10 mg cetirizine was evident by 1 h after treatment and was still apparent after 24 h. Although 20 mg epinastine was found to have a faster onset of action at 30 min after treatment, and the effects of 60 mg terfenadine appeared to be comparable to those of cetirizine, analysis of area under the curve for wheal responses at 0–24 h for all drugs demonstrated that cetirizine was the most potent and loratadine the least potent of all, with a rank order of potency of cetirizine > epinastine > terfenadine > ebastine > fexofenadine > loratadine > placebo.

Table 2. Assessment of bioequivalence between cetirizine and levocetirizine

Measure	Parameter (unit)	Mean levocetirizine ($n=18$)	Mean cetirizine ($n=18$)	Ratio	90% confidence interval of ratio	
Wheal area	AUC-Inh$_{0-32\ h}$ (%.h)	1938	1314	1.47	1.16	1.79
	AUC-wheal$_{0-32\ h}$ * (mm^2.h)	742	820	0.91	0.79	1.04
	A_{max} * (%)	92.1	88.3	1.04	1.01	1.08
Flare area	AUC-Inh$_{0-32\ h}$ (%.h)	1946	1877	1.04	0.85	1.22
	AUC-flare$_{0-32\ h}$ * (mm^2.h)	10413	10919	0.95	0.74	1.23
	A_{max} * (%)	95.2	94.3	1.01	0.99	1.03

*Detransformed geometric mean ratio and corresponding 90% confidence interval.

Furthermore, these authors demonstrated that cetirizine caused greater than 95% inhibition of the histamine-induced wheal response in 13 of the 14 individuals investigated. Similarly, Simons et al. (20) have compared the inhibition profiles of several antihistamines on histamine-induced wheals and flares in 20 healthy white males, and have also demonstrated cetirizine to be the most potent of all the drugs investigated, with a rank order of potency of 10 mg cetirizine > 120 mg terfenadine > 60 mg terfenadine > 10 mg loratadine > 10 mg astemizole > 4 mg chlorpheniramine > placebo. These authors demonstrated that although the inhibitory effects of cetirizine on both the wheal and flare were apparent by 30 min after treatment and lasted over the period of 24 h investigated, the effect on wheal and flare was significant by 1 and 0.7 h, respectively, after treatment. However, these authors also demonstrated that cetirizine produced a maximum suppression of wheal area of 94% and flare area of 89% at 5 h after treatment. Coulie et al. (21) have suggested that the 30-min onset of action time noted for cetirizine in attenuating histamine-induced wheal and flare responses correlates with the time at which the concentration of this drug peaks in the plasma after its intake.

Several double-blind, randomized, crossover comparisons of cetirizine and placebo or other antihistamines in the management of urticaria have also demonstrated that cetirizine is significantly superior to placebo, terfenadine, and astemizole in providing faster/greater relief of pruritis, wheals, erythema, and overall symptoms of chronic urticaria (14). Similarly, studies of cetirizine in the nasal airways of healthy volunteers and patients with seasonal/perennial allergic rhinitis have demonstrated that this compound is significantly more efficacious than placebo, astemizole, ketotifen, loratadine, and terfenadine in also providing relief from symptoms of rhinitis (22, 23). Some studies of the effects of cetirizine in the nose, however, have provided information in accordance with the studies in the skin by demonstrating that the inhibitory effects of cetirizine in the nose are also evident at 1.5–24 h after intake (24, 25). Collectively, these studies in the skin and nose suggest that the antihistaminic effects of cetirizine, and its active enantiomer levocetirizine, are unlikely to be organ specific and are probably dependent on the plasma concentrations to which they can rise in different allergic conditions where histamine is known to play a prominent pathogenic role.

In conclusion, this study has demonstrated that single doses of cetirizine (5 mg) and its composite enantiomers levocetirizine (2.5 mg) or ucb 28557 (2.5 mg) are safe and well tolerated in healthy volunteers. Furthermore, this study has suggested that the antihistaminic properties noted for cetirizine in the management of allergic skin conditions are likely to be due to the levocetirizine enantiomer, since this compound presents very similar pharmacodynamic profiles to those observed for cetirizine. Nevertheless, this remains to be confirmed in individuals with allergic skin conditions. The use of levocetirizine as a safe, well-tolerated, and highly efficacious drug at only half the recommended dose of cetirizine, for the treatment of allergic conditions, may be a distinct possibility in the future.

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References

1. Friedmann PS. Assessment of urticaria and angio-oedema. Clin Exp Allergy 1999;**29 Suppl 3**:109–112.
2. Greaves MW, Sabroe RU. Allergy and the skin. I. Urticaria. BMJ 1998;**316**:1147–1150.
3. Ormerod AD. Urticaria – pathophysiology. In: Holgate ST, Church MK, editors. Allergy. London: Mosby Wolfe 1995:21.1–21.12.
4. Atkins PC, Schwartz LB, Adkinson NF, von Allmen C, Valenzano M, Zweiman B. *In vivo* antigen-induced cutaneous mediator release: simultaneous comparisons of histamine, tryptase and prostaglandin D_2 release and the effect of oral corticosteroid administration. J Allergy Clin Immunol 1990;**86**:360–370.
5. Atkins PC, von Allmen C, Valenzano M, Olson R, Shalit M, Zweiman B. Determinants of *in vivo* histamine release in cutaneous allergic reactions in humans. J Allergy Clin Immunol 1990;**86**:371–379.
6. Bousquet J, Godard P, Michel FB. Antihistamines in the treatment of asthma. Eur Respir J 1992;**5**:1137–1142.
7. Howarth PH. Histamine and asthma: an appraisal based on specific H_1-receptor antagonism. Clin Exp Allergy 1990;**20S**:31–41.
8. Pipkorn U. Mediators and nasal allergy. Clin Exp Allergy 1989;**26**:585–589.
9. White MV, Slater JE, Kaliner MA. Histamine and asthma. Am Rev Respir Dis 1987;**135**:1165–1176.
10. Rimmer SJ, Church MK. The pharmacology and mechanisms of action of histamine H_1-antagonists. Clin Exp Allergy 1990;**20S**:3–17.
11. Simons FER. Non-cardiac adverse effects of antihistamines (H_1-receptor antagonists). Clin Exp Allergy 1999;**29 Suppl 3**:125–132.
12. Lawlor F. Urticaria – diagnosis and treatment. In: Holgate ST, Church MK, editors. Allergy. London: Mosby Wolfe 1995:22.1–22.12.
13. Kobza-Black A. H_1 antagonists in the management of the itch of urticarias. Skin Pharmacol 1992;**5**:21–24.
14. Spencer CM, Faulds D, Peters DH. Cetirizine: a reappraisal of its pharmacological properties and therapeutic use in selected allergic disorders. Drugs 1993;**46**:1055–1080.
15. Snyder SH, Snowman AM. Receptor effects of cetirizine. Ann Allergy 1987;**59**:4–8.
16. Rihoux JP. Antihistamines. In: Rihoux JP, editor. The allergic reaction. 2nd edn. Brussels: Imiprimerie Lielens 1993:255–301.
17. Schuirmann D. A comparison of the two one-sided tests procedure and power approach for assessing the bioequivalence of average bioavailability. J Pharmacokinet Biopharm 1987;**15**:657–680.
18. Steinijans VW, Hauschke D. Update on the statistical analysis of bioequivalence studies. Int J Clin Pharmacol 1990;**28**:105–110.
19. Grant JA, Danielson L, Rihoux JP, DeVos C. A double-blind, single-dose, crossover comparison of cetirizine, ebastine, epinastine, fexofenadine, terfenadine, and loratadine, versus placebo: suppression of histamine-induced wheal and flare response for 24 h in healthy male subjects. Allergy 1999;**54**:700–707.
20. Simons FER, McMillan JL, Simons KJ. 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 hours in normal subjects. J Allergy Clin Immunol 1990;**86**:540–547.
21. Coulie P, Ghys L, Rihoux JP. Inhibitory effects of orally or sublingually administered cetirizine on histamine-induced wheals, flares and their correlation with cetirizine plasma concentrations. J Int Med Res 1991;**19**:174–179.
22. Lockey RF, Widlitz MD, Mitchell DQ, et al. Comparative study of cetirizine and terfenadine versus placebo in the symptomatic management of seasonal allergic rhinitis. Ann Allergy Asthma Immunol 1996;**76**:448–454.
23. Campoli-Richards DM, Buckley MM-T, Fitton A. Cetirizine. A review of its pharmacological properties and clinical potential in allergic rhinitis, pollen-induced asthma and chronic urticaria. Drugs 1990;**40**:762–781.
24. Frossard N, Lacronique J, Melac M, et al. Onset of action in the nasal antihistaminic effect of cetirizine and loratadine in patients with allergic rhinitis. Allergy 1997;**52**:205–209.
25. Frossard N, Benabdesselam O, Melac M, Glasser N, Lacronique J, Pauli G. Nasal effect of cetirizine and loratadine at 24 hours in patients with allergic rhinitis. Am J Ther 1998;**5**:307–311.