

# Twenty-four-hour activity and consistency of activity of levocetirizine and desloratadine in the skin

Ashok Purohit, Michel Melac,<sup>1</sup> Gabrielle Pauli & Nelly Frossard

INSERM U425, Service de Pneumologie, Hôpitaux Universitaires, Strasbourg and Faculté de Pharmacie, BP 24, Illkirch, and <sup>1</sup>UCB Pharma, Nanterre, France

**Aim** Levocetirizine, the active enantiomer of cetirizine, and desloratadine, the active metabolite of loratadine, are two recently introduced anti-H<sub>1</sub> agents. We set out to compare their antihistaminic activity in the skin for 24 h in a double-blind, randomized cross-over trial.

**Methods** The skin reaction to histamine administered by prick tests (100 mg ml<sup>-1</sup>) was measured by the surface areas of weals and flares for 24 h [before treatment, 0.5, 1, 2, 3, 4, 6, 8, 10, 12 and 24 h after a single dose of levocetirizine (5 mg), desloratadine (5 mg) or placebo] in 18 healthy volunteers (34.8 ± 9.4 years; 14 women). The areas under the curves (AUC) of the weal and flare areas as a function of time were compared by ANOVA.

**Results** A highly significant overall treatment effect ( $P < 0.0001$ ) was observed and both weals and flares were inhibited. The pairwise comparisons showed that the activity of levocetirizine and desloratadine was significantly superior to that of placebo ( $P < 0.0001$ ), and the activity of levocetirizine was significantly superior to that of desloratadine ( $P < 0.0001$ ). 'Total' weal inhibition ( $\geq 95\%$ ) occurred only with levocetirizine. Median values of maximal weal inhibition were 44.2% with placebo, 55.0% with desloratadine and 100% with levocetirizine. The time to maximal weal inhibition was 4 h (median value) for all three study drugs, but scattered over a wider range for desloratadine (3–24 h) than levocetirizine (2–4 h). With desloratadine, five of 18 (28%) subjects reached weal inhibition of at least 70% at between 3 and 10 h, whereas with levocetirizine all subjects [18/18 (100%)] reached this level of weal inhibition at between 1 and 3 h. The median duration of 70% weal inhibition was zero with placebo and desloratadine, and was 21.4 h with levocetirizine ( $P < 0.0001$  between the three study drugs, and  $P < 0.0001$  between the two active drugs). No uncommon adverse events were reported, and no subject withdrew from the study due to an adverse event.

**Conclusion** This study shows that the activity of levocetirizine in suppressing skin reactivity to histamine was clearly superior to that of desloratadine for 24 h after a single dose. In addition, its activity was more consistent and lasted longer.

**Keywords:** anti-histamine, allergy, weal and flare model, rhinitis

## Introduction

The activity of H<sub>1</sub>-receptor antagonists in the relief of symptoms of chronic urticaria as well as of allergic rhinitis is now well established.

Levocetirizine, the R-enantiomer of cetirizine, is an antihistamine with high affinity and selectivity for H<sub>1</sub>-

receptors. *In vitro* binding studies using cloned human H<sub>1</sub>-receptors showed that its affinity was twice that of cetirizine [1]. Its selectivity is similar to that reported for both the racemic compound, cetirizine, and for the S-isomer. Two pharmacodynamic studies in healthy volunteers [2, 3] suggest that levocetirizine is the active enantiomer of cetirizine. In the skin, the maximal inhibition of a weal and flare reaction induced by histamine is equivalent with levocetirizine 2.5 mg and cetirizine 5 mg; moreover, inhibition over a 32-h period is reported to be significantly better with levocetirizine than cetirizine, and the activity of the S-isomer (2.5 mg)

Correspondence: Nelly Frossard, Neuroimmunopharmacologie Pulmonaire, INSERM U 425, BP 24, 67401 Illkirch Cedex, France. Tel.: + 33 3 9024 4196; Fax: + 33 3 9024 4309, E-mail: nelly.frossard@pharma.u-strasbg.fr

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similar to that of placebo [2]. In the nose, the median histamine nasal threshold concentration quadruples after a single administration of levocetirizine (5 mg), as with cetirizine, whereas activity of the S-isomer is similar to that of placebo [3]; median nasal pressure and sneezing are also significantly reduced by levocetirizine and cetirizine, but not by the S-isomer. The antihistaminic effect of levocetirizine lasts for 24 h. In addition, it is as rapidly absorbed and active as cetirizine, its distomer, according to the bioequivalence analysis of the pharmacokinetic parameters [4]. In our study, levocetirizine was used at 5 mg.

Desloratadine (descarboethoxyloratadine) is the orally active major metabolite of loratadine, with nonsedating, long-acting, and selective peripheral H<sub>1</sub>-receptor antagonistic activity [5–7]. It is indicated (5 mg daily) for the relief of symptoms associated with seasonal allergic rhinitis or chronic urticaria [8–11]. Its pharmacodynamic activity is similar to that of its parent, loratadine. Its antihistaminic effect lasts for 24 h [5] and its elimination half-life after oral administration ranges from 17 to 30 h [6, 12].

A previous study of the activity of single doses of levocetirizine (5 mg) on histamine-induced skin reactions in healthy male subjects compared its activity with that of other antihistamines at their therapeutic dosage: ebastine (10 mg), fexofenadine (180 mg), loratadine (10 mg) and mizolastine (10 mg) [13]. The assessment of their global anti-H<sub>1</sub> activity over 24 h showed that levocetirizine had the greatest activity and consistency of all the antihistamines under investigation: the histamine-induced weal and flare surface areas (AUC<sub>(0–24 h)</sub>) were significantly lower – both statistically and pharmacologically – after levocetirizine than after the other antihistamine treatments.

The aim of this study was to compare the activity on histamine-induced skin reactions of levocetirizine and desloratadine at their therapeutic dosage of 5 mg each and of placebo for 24 h after a single oral dose in 18 healthy volunteers. To assess objectively the reaction to histamine skin prick tests (100 mg ml<sup>-1</sup>), we measured the surface areas of the weal and flare for 24 h (before treatment, 30 min, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, 10 h, 12 h and 24 h) after a single dose. We compared the two active drugs as to the frequency of 'total' weal inhibition (corresponding to a weal inhibition of at least 95%) for each treatment and at each time point, as well as the frequency of subjects with total inhibition at one or more time points to evaluate the consistency of their activity. In addition, we also assessed and compared the maximal weal inhibition and time to maximal weal inhibition, the time to a weal inhibition of at least 70%, and the time during which the weal inhibition was at least 70% for each treatment.

## Methods

### Subjects

The study included 18 healthy volunteers (14 women, four men, aged 18–50 years, mean age 34.8 ± 9.4 years). At inclusion, they had no clinically relevant diseases, according to their medical history and examination including ECG and laboratory tests, a normal body mass index (between 19 and 29), no personal history of allergy, and a negative test for common specific IgEs (Phadi-atop<sup>®</sup>; Pharmacia & Upjohn, St. Quentin en Yvelines, France). No concomitant medication was permitted for 2 weeks before inclusion or during the study, with the exception of contraceptive pills and paracetamol. Subjects were asked to avoid skin irritants or UV exposure for 48 h before each visit. The wash-out period after intake of systemic corticosteroids was at least 4 weeks. All signed a written informed consent to participate in the study, which was approved by the hospital ethics committee.

### Study design

This was a phase I double-blind, randomized, placebo-controlled, single oral dose, three-way cross-over trial to compare the effects of levocetirizine (5 mg) and desloratadine (5 mg) on histamine-induced weals and flares for 24 h. The tests were separated by at least 14 days. In each treatment period, subjects underwent a histamine (100 mg ml<sup>-1</sup>) skin prick test (Prick lancet; Stallergènes, Les Ulis, France) at time 0 between 07.30 and 09.30 h. They then took at random one capsule of either levocetirizine 5 mg, desloratadine 5 mg, or placebo, identical in appearance to ensure double-blinding, with a glass of water. They then underwent histamine skin prick tests (100 mg ml<sup>-1</sup>) again at times 0.5, 1, 2, 3, 4, 6, 8, 10, 12 and 24 h.

### Antihistamine activity

Activity was assessed by the surface areas of skin weals and flares at each time point after treatment. Fifteen minutes after each skin prick test, the weal and flare areas induced by histamine were outlined directly on the forearm and then traced onto adhesive transparent paper. The areas were scanned, entered into computer software (Adobe Photoshop, Adobe Systems, San Jose, California), and analysed with the public domain NIH Image program (US National Institutes of Health, Bethesda, MD, USA). They were measured twice, nonconsecutively. Post-treatment histamine time–response curves were constructed.

### Frequency of 'total' inhibition of the weal

The weal was considered as 'totally' inhibited when it was <95% of its value before the study drug dose. For

each time point and each treatment period, the percentage of inhibition and the number of subjects with 'totally' inhibited weals were calculated.

#### *Maximal weal inhibition (%) and time to maximal weal inhibition*

Maximal weal inhibition was the highest value of weal inhibition between 0 and 24 h. The time to reach maximal weal inhibition was determined at this point.

#### *Time to 70% inhibition and duration of treatment effect*

The time to reach 70% inhibition was defined as the exact time at which the weal inhibition crossed the 70% level. The duration of effect is the time during which weal inhibition remained at least 70%. It was calculated by interpolation from each subject's curve.

#### *Safety measurements*

Adverse events were described by their type, source, severity, frequency, relation to the tested drug, and finally their seriousness.

#### *Expression of results and statistical analysis*

Calculation of sample size was based on the results of a previous study [14] at the same centre with the same design. In that study, weal inhibition was 77% better with cetirizine than with placebo (calculated from the AUC of the weals). Levocetirizine was presumed to be at least as potent as cetirizine [13]. To detect a difference of at least 15% between levocetirizine and desloratadine (i.e. an improvement of 62% compared with placebo for desloratadine) with a power of 90% and a two-sided significance level of 5%, 18 subjects were required.

Areas ( $\text{mm}^2$ ) of weals and flares are presented as the mean  $\pm$  SEM for each time and treatment. The primary efficacy variables were the areas under the time-response curves (AUC) of weal and flare areas from 0 to 24 h after treatment intake, expressed as  $\text{mm}^2 \text{h}^{-1}$ . AUC were calculated with the trapezoidal rule ( $\text{mm}^2 \text{h}^{-1}$ ). The analysis used an ANOVA model for cross-over design, including the subject, sequence, period and treatment to compare between the AUC for weals and for flares. We used a closed testing procedure to deal with the problem of multiple comparisons: the overall treatment effect was tested first with an  $\alpha$  level of 5% and, if significant, each pairwise comparison was tested at 5% [15]. The treatment effect was estimated by calculating the difference in the least squares means for each pairwise comparison, and its associated 95% confidence interval. The comparison between levocetirizine

and desloratadine was considered to be the comparison of primary interest.

Nonparametric methods were used to analyse the time until weal inhibition reached at least 70% and the time during which it remained at least 70%: the Friedman test for overall treatment effect and sign tests for pairwise comparisons. We also present the coefficient of dispersion for the maximal weal inhibition and time to maximal weal inhibition (= 95%). In addition, the proportion of subjects reaching 'total' inhibition at one or more time points was compared for the three treatments with a Cochran Q-test. The pairwise comparisons were then performed with MacNemar tests.

An  $\alpha$  value of 5% (type I error) was used as the significance level, and all tests were two-sided.

## Results

### *Weal inhibition over time*

Weal areas before treatment did not differ between the three treatment periods (Table 1). The largest mean weal areas were obtained with placebo regardless of time point (Figure 1). Weal areas decreased slightly within 4 h and then remained high and globally stable through 24 h. Inhibition did not exceed 25%. Placebo treatment was associated with the highest mean area under the time-response curve (Table 2;  $P < 0.001$  between placebo and the two active drugs;  $P < 0.0001$  between levocetirizine and desloratadine).

The smallest mean weal areas were obtained with levocetirizine (Figure 1) and the time-response curve had the lowest mean AUC value (Figure 2, Table 2). Inhibition was maximal at 4 h postdose and was stable for 12 h, then decreased slightly to remain at  $>65\%$  at 24 h. The desloratadine curve was situated between the other two (Figure 1), with a mean AUC between the other two (Figure 2, Table 2). Inhibition reached its maximum point after 4 h and was stable for the 24 h postdose. The three curves of the weal areas never crossed.

The difference in the weal response between treatments was highly significant (Figure 2), with activity in

**Table 1** Weal and flare areas in the three treatment groups before treatment with either placebo, levocetirizine 5 mg or desloratadine 5 mg (time 0).

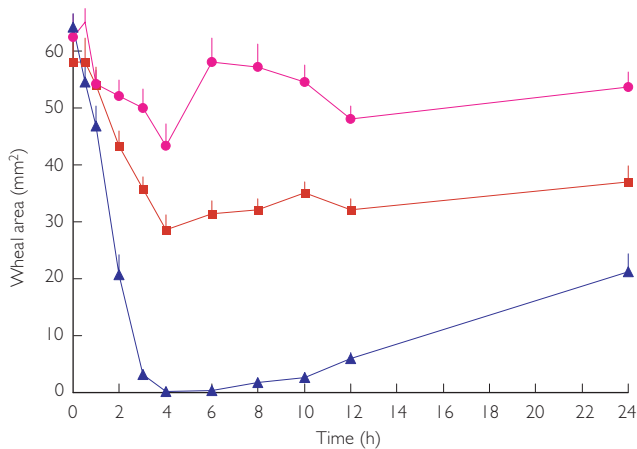
Before treatment	Weal area ( $\text{mm}^2$ )	Flare area ( $\text{mm}^2$ )
Placebo	62.5 $\pm$ 4.1	954.4 $\pm$ 77.6
Levocetirizine 5 mg	64.3 $\pm$ 5.6	962.2 $\pm$ 92.5
Desloratadine 5 mg	58.2 $\pm$ 5.4	952.1 $\pm$ 83.5

Means and SEM were calculated in the 18 patients. No difference was observed between treatment groups.

**Table 2** AUC values of weal and flare areas in the three treatment groups over 24 h.

AUC of weal/flare area ( $\text{mm}^2 \text{h}^{-1}$ )	Placebo	Desloratadine 5 mg	Levocetirizine 5 mg
Mean weal $\pm$ SEM	1255.8 $\pm$ 45.9	851.7 $\dagger$ $\pm$ 39.4	281.9* $\dagger$ $\pm$ 25.7
Mean flare $\pm$ SEM	25523.0 $\pm$ 1622.4	17758.5 $\dagger$ $\pm$ 1244.2	5810.8* $\dagger$ $\pm$ 794.2

Means and SEM were calculated in the 18 patients.  $\dagger P < 0.0001$  vs. placebo; \* $P < 0.0001$  vs. desloratadine.



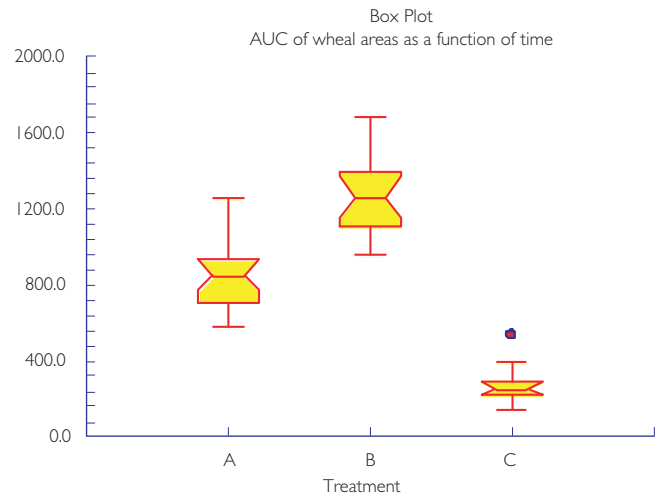
**Figure 1** Time-response curves of the weal response to histamine after treatment with levocetirizine 5 mg ( $\blacktriangle$ ), desloratadine 5 mg ( $\blacksquare$ ), and placebo ( $\bullet$ ). Points are means, and bars are SEM of the weal areas ( $\text{mm}^2$ ) measured in 18 healthy volunteers.

the following order of magnitude: levocetirizine > desloratadine > placebo ( $P < 0.0001$ ).

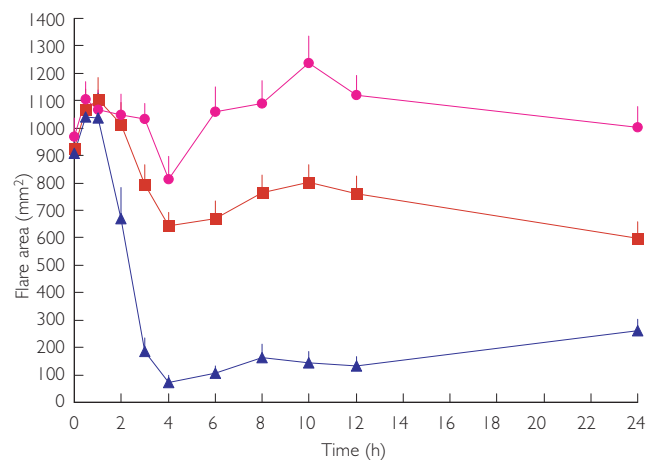
#### Flare inhibition over time

The profiles of the curves for the mean flare areas were similar to those for the weal areas (Figure 3). The flare areas before treatment did not differ between the three treatment periods (Table 1). After placebo treatment, flare areas decreased slightly within 4 h and then remained high and globally stable through 24 h (Figure 3). Inhibition did not exceed 25%. Placebo treatment was associated with the highest mean time-response AUC (Table 2;  $P < 0.001$  between placebo and the two active drugs;  $P < 0.0001$  between levocetirizine and desloratadine).

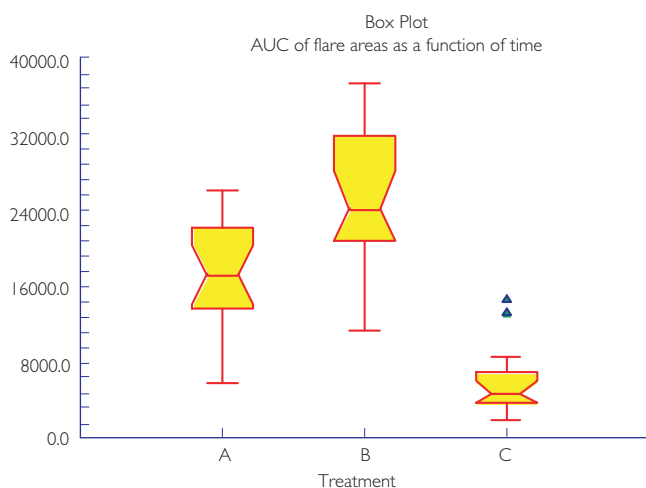
In contrast, the smallest mean flare areas were obtained with levocetirizine (Figure 3) and the time-response curve had the lowest mean AUC value (Figure 4). Inhibition was maximal at 4 h postdose and was stable for 12 h, then decreased slightly to remain at >70% inhibition at 24 h. The desloratadine curve was situated between the other two (Figure 3), with a mean AUC between the other two (Figure 4). Inhibition reached its maximum point after 4 h, and remained stable during the 24 h postdose. The three curves of the flare areas never crossed.



**Figure 2** AUC of the weal areas as a function of time for levocetirizine (C), desloratadine (A) and placebo (B). Box plots are limited by the first and third quartiles, with median (second quartile) as the horizontal line inside the box. The vertical lines above and below the box are 'whiskers' cut at adjacent values, calculated as the quartile  $\pm 1.5 \times$  the interquartile. The notch amplitude around the median line corresponds to the confidence interval of the median, which allows a comparison between two boxes: if intervals separate completely, distributions do show a difference. Results came from 18 healthy volunteers.



**Figure 3** Time-response curves of the flare response to histamine after treatment with levocetirizine 5 mg ( $\blacktriangle$ ), desloratadine 5 mg ( $\blacksquare$ ), and placebo ( $\bullet$ ). Points are means, and bars are SEM of the flare areas ( $\text{mm}^2$ ) measured in 18 healthy volunteers.



**Figure 4** AUC of the flare areas as a function of time for levocetirizine (C), desloratadine (A) and placebo (B). Box plots are limited by the first and third quartiles, with median (second quartile) as the horizontal line inside the box. The vertical lines above and below the box are 'whiskers' cut at adjacent values, calculated as the quartile  $\pm 1.5 \times$  the interquartile. The notch amplitude around the median line corresponds to the confidence interval of the median, which allows a comparison between two boxes: if intervals separate completely, distributions do show a difference. Results came from 18 healthy volunteers.

The difference in the flare response between treatments was highly significant (Figure 4), with activity in the following order of magnitude: levocetirizine > desloratadine > placebo ( $P < 0.0001$ ).

#### Frequency of 'total' weal inhibition ( $\geq 95\%$ )

The proportion of subjects with weal inhibition that exceeded 95% differed significantly between the three treatment groups. The weal was never 'totally' inhibited with placebo (0/18) or with desloratadine (0/18). 'Total' inhibition occurred only with levocetirizine: 4 h after levocetirizine treatment, 'total' inhibition was reached for all subjects (18/18). Two subjects reached 'total' inhibition at 2 h and four subjects remained 'totally' inhibited at 12 h.

#### Maximal weal inhibition (%) and time to maximal weal inhibition

Median values of maximal weal inhibition were 44.2% with placebo, 55% with desloratadine, and 100% with levocetirizine. Variability of maximal weal inhibition was lower with levocetirizine than with desloratadine and placebo. With levocetirizine, 17 of 18 subjects reached a weal inhibition of 100% at one time point at least. The remaining subject had a maximal inhibition of 96.8%.

The time to maximal weal inhibition was 4 h (median value) for each of the three study periods. For desloratadine, the time to peak ranged from 3 to 24 h. This high variability was confirmed by a high coefficient of dispersion value (0.750). With levocetirizine, the peak was always reached between 2 and 4 h, a good consistency also reflected by the low coefficient of dispersion (0.175).

#### Time to reach a weal inhibition of at least 70%

The time to weal inhibition of at least 70% differed significantly between the three study drugs ( $P < 0.0001$ ) and between the two active drugs ( $P < 0.0001$ ). Weal inhibition never reached 70% under placebo. With desloratadine, five of 18 subjects (27.8%) reached weal inhibition of at least 70%, in a period that ranged from 3 h to 10 h. All subjects reached a weal inhibition of at least 70% between 1 and 3 h with levocetirizine.

#### Duration of effect

The time during which weal inhibition was at least 70% differed significantly between the three study drugs ( $P < 0.0001$ ) and between the two active treatments ( $P < 0.0001$ ). The median time during which weal inhibition was at least 70% was zero with placebo and with desloratadine, while the median 70% inhibition with levocetirizine lasted 21.4 h. The median difference between the two active drugs was 19.5 h, with a 95% confidence interval of 15.4 to 21.0 h.

#### Safety results

No uncommon adverse event was reported, and no subject withdrew from the study due to an adverse event. Sixteen of 18 randomized subjects reported at least one adverse event: fatigue, somnolence, headache and/or thirst. These were reported most frequently after active treatments and only once under placebo (headache). None was serious, although they were considered to be related to the study drugs. Fatigue, for example, was reported by two subjects with desloratadine, two with levocetirizine and none with placebo.

#### Discussion

Our study reports the effectiveness in inhibiting skin reactivity to histamine of two new antihistamines, levocetirizine and desloratadine, at the therapeutic dosage of 5 mg, compared with placebo for a 24-h period: we found significantly greater activity by levocetirizine than desloratadine. In addition, our study shows that the activity of levocetirizine was more consistent: more patients had total weal inhibition, maximal weal inhibition was



higher, and time was shorter to maximal weal inhibition and to 70% weal inhibition. Finally, weal inhibition of at least 70% lasted much longer.

In this study, a cross-over design was chosen to minimize variability by ensuring within-subject treatment comparisons. This worked very well for our purposes, with single-dose intake of medication and a 2-week wash-out interval between treatment periods to prevent any carry-over effect. Activity of H<sub>1</sub>-receptor antagonists was assessed by the inhibition of the weal and flare reaction induced by histamine skin prick tests; this criterion is probably the most reliable method for assessing cutaneous histamine antagonistic activity in humans [14, 16, 17]. The time-response design allowed us to compare the relative activity of the drugs as well as the consistency of their activity by assessment of the frequency of total and 70% inhibition of the weal [18, 19].

The two active treatments, levocetirizine and desloratadine at the therapeutic dosage of 5 mg each, both showed clearly significant activity compared with placebo. However, the surface areas of weals and flares were significantly lower over time for levocetirizine than desloratadine, suggesting better activity by the former. Maximal inhibition of the areas of weals and of flares differed greatly between drugs: whereas levocetirizine inhibited the weal by 95% and more in all volunteers, no such 'total' inhibition occurred under desloratadine, for which the median maximal inhibition was only 55%. This confirms that levocetirizine acts more effectively than desloratadine on skin weal reactivity, with an order of potency of levocetirizine > desloratadine > placebo. These activity findings are consistent with results previously reported for their congeners, cetirizine and loratadine [20, 21]. They also confirm previously reported results about the effect of levocetirizine in human skin, with an inhibitory activity exceeding that of loratadine [22]. In addition, results obtained with desloratadine are in agreement with findings previously reported for its parent, loratadine, by Grant *et al.* that maximal inhibition of histamine-induced (100 mg mL<sup>-1</sup>) weals and flares was reached at 4 h [21]. These results differ slightly from those previously published by Simons *et al.*, who used histamine (1 mg mL<sup>-1</sup>) and found loratadine to be maximally active at 5 h [20]. This slower maximal activity might be related to the metabolization of loratadine into the active desloratadine. Although studies of loratadine have found slightly different activity kinetics, the maximal inhibitory activity is nonetheless concordant in all studies, with about 50% maximal inhibition, compared with the 95% inhibition obtained with cetirizine [20, 21]. This is in total accordance with our present results with the enantiomer levocetirizine and the metabolite desloratadine.

Additionally, our study found that when treated with levocetirizine, all subjects had weals inhibited by at least

70% at between 1 and 3 h. When treated with desloratadine, only five of 18 subjects achieved this level of weal inhibition, and at between 3 and 10 h. This very significant difference between the two active drugs shows that levocetirizine became highly active more rapidly than desloratadine and suggests that its onset of action is earlier.

Moreover, the duration of high activity was markedly longer for levocetirizine: the median value of the time during which weal area was inhibited by at least 70% was zero with desloratadine and 21.4 h with levocetirizine. The maximum weal inhibition due to desloratadine was 55% and occurred most often at 4 h after drug intake, whilst after 24 h the level of inhibition was slightly lower, at 38%, similar to the duration of action seen with its parent compound, loratadine [13]. In contrast, levocetirizine reduced weal area by 100% at 4 h, and inhibition remained nearly 70% 24 h after drug intake. Levocetirizine thus showed high activity at 24 h, substantially more than desloratadine.

The consistency of activity, i.e. the activity that varied least between subjects, was demonstrated by the frequency of 'total' weal inhibition, defined as weal inhibition of at least 95%, by the maximal inhibition, and by the time to maximal inhibition. First, the frequency of total inhibition clearly differed between treatments. Total weal inhibition occurred only with levocetirizine and never with desloratadine. Second, 17 of the 18 subjects had 100% weal inhibition when treated with levocetirizine; the remaining subject had a maximal inhibition of 96.8%, whereas no subject reached 95% with desloratadine. Third, the time to peak activity of desloratadine ranged from 3 and 24 h, whereas the peak was always achieved between 2 and 4 h with levocetirizine. These findings show that the activity of levocetirizine is clearly more consistent than that of desloratadine. Hence, the effect of levocetirizine varied less than that of desloratadine. The consistency of levocetirizine activity that we found is in agreement with previous findings for its parent, cetirizine, also reported to have good consistency, better than that of ebastine or fexofenadine [14, 17, 23]. The different consistency in the activity of both drugs cannot, however, be explained by the need for biotransformation into the active metabolite, since desloratadine [6, 24] and levocetirizine [25] are both directly absorbed and active.

No serious adverse events occurred during the study. This is in accordance with the very low incidence of side-effects reported for both drugs and their parent congeners, cetirizine and loratadine. The most frequently reported events were fatigue, somnolence, headaches and dry mouth. No uncommon adverse events were reported, and no subject withdrew from the study due to an adverse event.

In conclusion, this study clearly shows that the activity of levocetirizine in suppressing skin reactivity to histamine is superior to that of desloratadine for 24 h after a single dose of 5 mg. In addition, levocetirizine was also more consistent, inducing total weal and flare inhibition in all subjects, unlike desloratadine, and inducing substantially longer high levels of inhibition.

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