Inflamm. res. 52 (2003) 424–427
1023-3830/03/100424-04
DOI 10.1007/s00011-003-1193-5



Inflammation Research

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

**K. J. Denham [1], P. Boutsiouki [1], G. F. Clough [1] and M. K. Church [1,2]**

[1] University of Southampton, Division of Infection, Inflammation and Repair, School of Medicine, Southampton, UK
[2] Southampton General Hospital, Dermatopharmacology Unit, South Block 825, Southampton SO16 6YD, UK, Fax: ++ 44 0 23 8070 4183, e-mail: mkc@soton.ac.uk

Received 21 May 2003; returned for revision 29 May 2003; accepted by M. Parnham 5 June 2003

**Abstract.** *Objective:* A previous study showed the inhibitory effects of loratadine on histamine-induced wheal, flare and itch in human skin to be very variable between individuals. It was hypothesised that this variability may have been due to differences in the rates of metabolism of loratadine to its active form, desloratadine. This double blind, crossover study examined the effects of desloratadine in 12 healthy volunteers. Levocetirizine was used as a comparator.
*Methods:*Desloratadine (5 mg), levocetirizine (5 mg) or placebo was taken orally 4 h before an intradermal injection of histamine (20 µl, 100 µM) or vehicle control into the forearm skin. Flare areas were assessed by scanning laser Doppler imaging before and at 30 s intervals for a period of 9 min. Wheal areas were measured by planimetry at 10 min. Itch was scored every 30 s for 5 min using a visual analogue scale.
*Results:* Following placebo administration, the mean (± SEM) wheal area at 10 min was 79.3 ± 6.9 $mm^2$, mean flare area for the first 5 min following challenge 26.6 ± 2.7$cm^2$, and itch score for the same period 48.5 ± 7.6%. The effects of desloratadine were variable between individuals, mean reductions in the wheal and flare areas being 17% ($P$ = 0.033) and 12% ($P$ = 0.036). Desloratadine did not reduce itch significantly. Levocetirizine was more consistent in its effects, mean reductions in wheal, flare and itch being 51%, 67% 78% respectively (all $P < 0.001$).
*Conclusions:* A single dose of 5 mg levocetirizine produced more consistent and greater inhibitory effects on histamine-induced wheal, flare and itch than did 5 mg desloratadine. The difference is suggested to reflect the basic pharmacokinetics of the two drugs.

**Key words:** Levocetirizine – Loratadine – Antihistamines – Wheal – Flare – Itch – Skin

*Correspondence to:* M. K. Church

## Introduction

Recent years have seen a change in $H_1$-antihistamines on the market throughout Europe. First, following the realisation of an association between cardiotoxicity and inhibition of the metabolism of terfenadine to its active metabolite, fexofenadine, by the cytochrome P450 enzyme CYP3A4 [1, 2], terfenadine was replaced on the market by fexofenadine. Second, although possessing minimal cardiotoxicity, loratadine is also effectively a pro-drug, being metabolised by the liver microsomal enzymes CYP3A4 and CYP2D6 to its active form, descarboethoxyloratadine (desloratadine) [3]. Desloratadine replaced loratadine on the market in 2001. Third, cetirizine is a racemic mixture of *S*- and *R*-enantiomers of which the *R*-enantiomer, levocetirizine, carries the majority of the histamine $H_1$-receptor blocking activity [4]. In late 2001, levocetirizine was marketed in its own right.

In a recent study [5], we compared the inhibitory effects of levocetirizine and loratadine against wheal, flare and itch provoked in human skin by the intradermal injection of histamine. Levocetirizine, 5 mg given orally 4 h before provocation, produced a consistent inhibition of all three responses. By contrast, loratadine, 10 mg also given orally 4 h before provocation, was shown to have a weaker effect which varied markedly between individuals. This finding of a weak and variable response with loratadine is consistent with the reports of others [6–8]. While the reason for the inconsistent efficacy of loratadine is not clear, one possible explanation is a variability in its hepatic metabolism to desloratadine, a compound which possesses 2.5 to 10 times the antihistaminic activity of loratadine in animal models [9, 10]. From the work of Hilbert and colleagues [11], peak plasma levels of loratadine occur $1\,^1/_2$ h after oral dosage while those of desloratadine are stated to occur in under three hours [9]. Thus, while an interval of 4 h between dosing and testing should have been sufficient for the absorption of loratadine and its metabolism to desloratadine, any delay in the hepatic metabolism of the parent drug in some individuals would result in a slower onset of action. Because of the design of the study, this would have been interpreted as a variability of effect.

To test this hypothesis, we assessed the inhibitory effects of desloratadine against wheal, flare and itch provoked in human skin by the intradermal injection of histamine in a double blind, placebo-controlled crossover study in 12 healthy volunteers. Levocetirizine was used as a comparator.

## Materials and methods

This study, which used an identical protocol to our previous study [5], was performed as a randomised, double-blind placebo-controlled crossover trial on 12 healthy male volunteers aged 19–35 with no history of allergy. Two weeks washout period was allowed between visits. The study was approved by the Southampton and South West Local Research Ethics Committee (study number 080/01) and all volunteers gave signed informed consent. Matching capsules of desloratadine (5 mg), levocetirizine (5 mg), or placebo were taken orally 4 h before each visit and subjects asked to refrain from eating, drinking caffeine-containing liquids or taking excessive exercise for 2 h before attending the laboratory, which was between 11.00 and 13.00 h in order to minimise intra-individual variation [5, 12]. Twenty microlitres of histamine (100 µM, Sigma, Poole, UK) or vehicle control (Ringer's solution, Fresenius Kabi Ltd, Basingstoke, UK), was injected intradermally, using a 27 gauge needle into the volar surface the forearm, one injection per arm. Changes in skin blood flow were assessed before and at intervals of 30 s for a period of 9 min after injection using scanning laser Doppler imaging (Moor Instruments Ltd, Axminster, UK). Flare areas were calculated from the calibrated images using the manufacturer's software [13]. The perimeter of the wheal at the end of the blood flux measurements at 10 min was traced onto an acetate sheet and the area calculated by planimetry. Itch sensation was scored every 30 s for a period of 10 min after histamine injection using a 10 cm visual analogue scale. All data are expressed as mean ± SEM and statistical analysis was performed using Student's t test for paired data. A probability value of $P < 0.05$ was taken as statistically significant.

## Results

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

Analysis of the time course of the development of the flare response (Fig. 1a), measured from the repeat scanning laser Doppler images, revealed that peak flare areas occurred 2–3 mins after the injection of histamine. Neither desloratadine nor levocetirizine altered this time course. The time course of the development of itch (Fig. 1b) showed the peak response to occur at around 1 min. Again, this time course was not altered by the drugs. For comparison of individual responses and treatment groups, mean values of flare area and itch scores between 0 and 5 min were calculated ($flare_{0-5}$ and $itch_{0-5}$, respectively).

Figure 2a shows that the inhibition of the $flare_{0-5}$ response by desloratadine was variable while that to levocetirizine was more consistent. The mean (± SEM) $flare_{0-5}$ of 21.8 ± 3.0 $cm^2$ measured after desloratadine dosing was significantly lower than that of 26.6 ± 3.0 $cm^2$ measured after placebo (12% reduction, $P = 0.036$). By comparison, levocetirizine, produced a more consistent and greater inhibitory effect, the mean $flare_{0-5}$ being 8.8 ± 2.1 $cm^2$ (67% reduction, $P < 0.001$). The difference between the inhibitory effects of desloratadine and levocetirizine was highly significant ($P < 0.001$). Intradermal injection of the saline vehicle caused a mean $flare_{0-5}$ area of 1.3 ± 1.1 $cm^2$ which was not significantly affected by either desloratadine or levocetirizine.

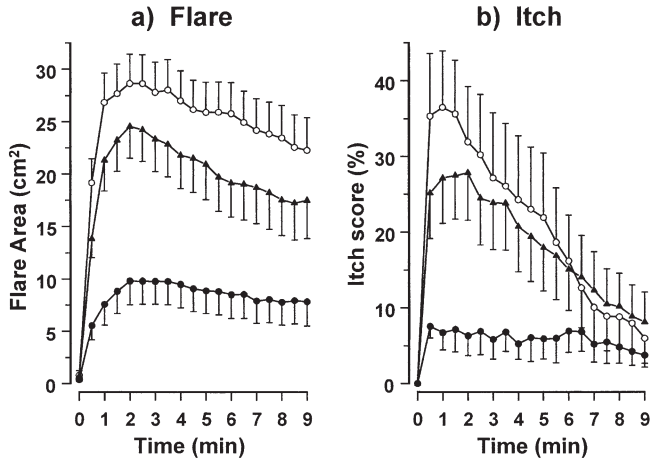


**Fig. 1. a)** Flare and **b)** itch responses to the intradermal injection of 20 µl of 100 µM histamine. The drugs taken orally 4 h before histamine injection were: placebo (open circles); 5 mg levocetirizine (closed circles); and, 10 mg loratadine (closed triangles). Flare areas were computed from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

The areas of the wheal responses, assessed at 10 min, were also variably reduced by desloratadine (Fig. 2b), the mean values being 79.3 ± 6.9 $mm^2$ for the placebo group and 66.1 ± 6.8 $mm^2$ following desloratadine (17% reduction, $P < 0.033$). Levocetirizine was again more consistent and effective (Fig. 2b), the mean wheal area being 39.2 ± 3.5 $mm^2$ (51% reduction, $P < 0.001$). The difference between the inhibitory effects of desloratadine and levocetirizine was statistically significant ($P = 0.007$).

The effect of desloratadine against itch was again variable (Fig. 2c), the mean $itch_{0-5}$ response following desloratadine administration being 23.8 ± 5.5% compared with 29.1 ± 7.2% for the placebo. The difference between these groups was not statistically significant ($P = 0.447$). In contrast, the mean $itch_{0-5}$ response following levocetirizine administration was 6.5 ± 2.4%, a 78% reduction of the placebo value ($P = 0.003$). The difference between the inhibitory effects of desloratadine and levocetirizine was statistically significant ($P = 0.02$).

## Discussion

In this single dose study, 5 mg desloratadine showed variable, but statistically significant, inhibitory effects on histamine-induced flare and wheal responses, but had no statistically significant effect on the itch response. In contrast, levocetirizine produced a more consistent and greater inhibitory effect on all of these parameters.

The variability of inhibitory responses produced by desloratadine were similar to those observed with loratadine in our previous study [5]. Thus, our hypothesis that this inconsistency of effect was due to variability in the rate of

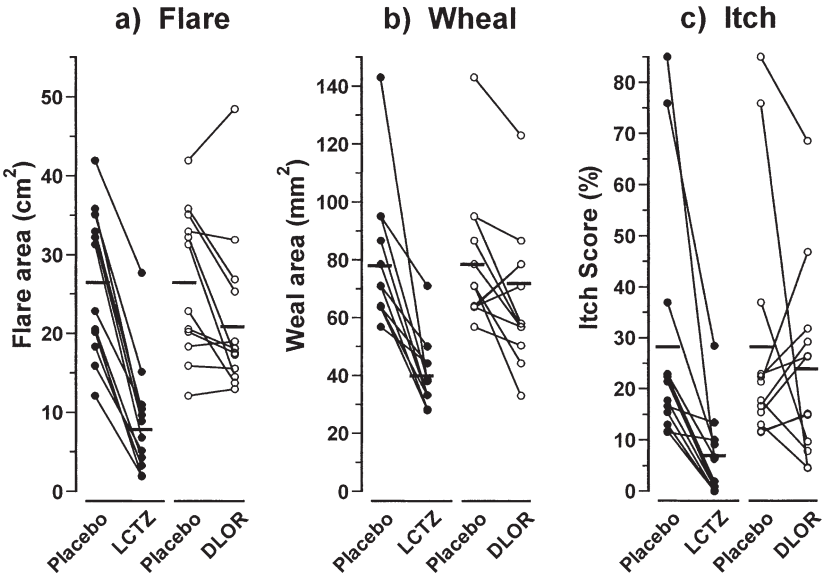


**Fig. 2.** Individual **a)** flare, **b)** wheal and **c)** itch responses to the intradermal injection of 20 µl of 100 µM histamine. The drugs taken orally 4 h before histamine injection were placebo, 5 mg levocetirizine (LCTZ) and 5 mg desloratadine (DLOR). The mean total flare areas over the first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

metabolism of loratadine to desloratadine appears to be incorrect. When trying to explain the difference in efficacy between desloratadine and levocetirizine in our study, it is more likely that other factors, particularly the physical characteristics of the drugs are important.

Before discussing these, it is important to clarify the conditions of our study. First, it was a single dose study with observations made at a time close to peak plasma levels, the $t_{max}$ values of desloratadine and levocetirizine being 3–4 h and 0.7–0.8 h respectively [14, 15]. Second, the concentration of histamine, 100 µM, used to elicit the wheal and flare response is higher than levels usually found within allergic responses [16]. Thus, the study acted as an indicator of in vivo efficacy under conditions where bioavailability, receptor binding affinity, volume of distribution and protein binding are likely to be the major determining factors. The bioavailability of the two drugs can be only estimated as the pharmacokinetic data after intravenous administration are not available: for desloratadine it is certainly less than 41% (as this is the % of the radioactive dose recovered in the urine in 10 days and it is known that the drug is extensively metabolized) [14], whereas for levocetirizine it is reported to be around 85% [15]. The receptor binding affinities (Ki) of the two drugs are comparable, desloratadine having a Ki of 0.4 nM while that of levocetirizine is 2 nM [17]. However, the volumes of distribution are markedly different. The absolute apparent volume of distribution ($V_z$/F) of desloratadine following a single 5 mg dose is 2911 litres [14], which, assuming a standard body weight of 70 kg, equates to ~40 l/kg. In comparison, the apparent volume of distribution of levocetirizine if 0.4 l/kg [18]. Further, the extent of protein binding of desloratadine is ~85% [14] while that of levocetirizine is 95% [15]. From simple calculations performed from these data, it may be predicted that, under the conditions of our study, a 5 mg dose of levocetirizine would be more effective in blocking the effects of histamine than would be a similar dose of desloratadine. This is reflected in the results obtained.

From our study, it is clear that levocetirizine is the more effective drug when given as a single dose, as would be the case in the treatment of acute allergic responses. However, care must be taken in extrapolating our data to the use of the drugs for prolonged therapy of chronic allergic diseases. When using multiple doses, other pharmacokinetic factors must be taken into consideration. The plasma half-life of desloratadine of 21–24 h [19] is longer than that of levocetirizine, around 7 h [15]. Also, the duration of binding of desloratadine to the $H_1$-receptor ($t_{1/2}$ > 6 h) [20] is longer than that of levocetirizine ($t_{1/2}$ ~2 h) [21].

In conclusion, in this single dose study, 5 mg levocetirizine produced more consistent and greater inhibitory effects on histamine-induced wheal, flare and itch than did 5 mg desloratadine. The difference is suggested to reflect the basic pharmacokinetic profiles of the drugs.

*Acknowledgements:* This study was supported by an educational grant from UCB Pharma.

## References

[1] Davies AJ, Harindra V, McEwan A, Ghose RR. Cardiotoxic effect with convulsions in terfenadine overdose. Br Med J 1989; 298: 325.

[2] Yun CH, Okerholm RA, Guengerich FP. Oxidation of the antihistaminic drug terfenadine in human liver microsomes. Role of cytochrome P-450 3A(4) in N-dealkylation and C-hydroxylation. Drug Metab Dispos 1993; 21: 403–9.

[3] Yumibe N, Huie K, Chen KJ, Snow M, Clement RP, Cayen MN. Identification of human liver cytochrome P450 enzymes that metabolize the nonsedating antihistamine loratadine. Formation of descarboethoxyloratadine by CYP3A4 and CYP2D6. Biochem Pharmacol 1996; 51: 165–72.

[4] Devalia JL, De Vos C, Hanotte F, Baltes E. A randomized, double-blind, crossover comparison among cetirizine, levocetirizine, and ucb 28557 on histamine-induced cutaneous responses in healthy adult volunteers. Allergy 2001; 56: 50–7.
[5] Clough GF, Boutsiouki P, Church MK. Comparison of the effects of levocetirizine and loratadine on histamine-induced wheal, flare, and itch in human skin. Allergy 2001; 56: 985–8.
[6] Frossard N, Melac M, Benabdesselam O, Pauli G. Consistency of the efficacy of cetirizine and ebastine on skin reactivity. Ann Allergy Asthma Immunol 1998; 80: 61–5.
[7] Bayramgurler D, Bilen N, Apaydyn R, Altintas L, Sal G, Dokmeci S et al. Effects of acrivastine, loratadine and cetirizine on histamine-induced wheal and flare responses. Clin Exp Dermatol 1999; 24: 407–11.
[8] Grant JA, Danielson L, Rihoux JP, De Vos 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: 700–7.
[9] Kreutner W, Hey JA, Anthes J, Barnett A, Young S, Tozzi S. Preclinical pharmacology of desloratadine, a selective and nonsedating histamine H1 receptor antagonist. 1st communication: receptor selectivity, antihistaminic activity, and antiallergenic effects. Arzneimittelforschung 2000; 50: 345–52.
[10] Kreutner W, Hey JA, Chiu P, Barnett A. Preclinical pharmacology of desloratadine, a selective and nonsedating histamine H1 receptor antagonist. 2nd communication: lack of central nervous system and cardiovascular effects. Arzneimittelforschung 2000; 50: 441– 8.
[11] Hilbert J, Moritzen V, Parks A, Radwanski E, Perentesis G, Symchowicz S et al. The pharmacokinetics of loratadine in normal geriatric volunteers. J Int Med Res 1988; 16: 50–60.
[12] Clough GF, Voegeli D, Bennett A, Church MK. A study of the inflammatory response in human skin using scanning laser Doppler imaging. International Journal of Microcirculation and Clinical Experimentology 1997; 17: 211.
[13] Clough GF, Bennett AR, Church MK. Effects of $H_1$-antagonists on the cutaneous vascular response to histamine and bradykinin: a study using scanning laser Doppler imaging. Br J Dermatol 1998; 138: 806–14.
[14] Schering Corporation. Clarinex (Desloratadine) Tablets Approval package. US Food and Drug Administration, Center for Drug Evaluation and Research, Application Number 21–165. 2001.
[15] Benedetti MS, Plisnier M, Kaise J, Maier L, Baltes E, Arendt C et al. Absorption, distribution, metabolism and excretion of [14C] levocetirizine, the Renantiomer of cetirizine, in healthy volunteers. Eur J Clin Pharmacol 2001; 57: 571–82.
[16] Petersen LJ, Church MK, Skov PS. Histamine is released in the wheal but not the flare following challenge of human skin in vivo – a microdialysis study. J Invest Dermatol 1995; 105: 50.
[17] Gillard M, Christophe B, Wels B, Peck MJ, Massingham R, Chatelain P. $H_1$-antagonists: receptor affinity versus selectivity. Inflamm Res 2003; 52 Suppl 1: S49–S50.
[18] Baltes E, Coupez R, Giezek H, Voss G, Meyerhoff C, Strolin BM. Absorption and disposition of levocetirizine, the eutomer of cetirizine, administered alone or as cetirizine to healthy volunteers. Fundam Clin Pharmacol 2001; 15: 269–77.
[19] Henz BM. The pharmacologic profile of desloratadine: a review. Allergy 2001; 56 Suppl 65: 7–13.
[20] Anthes JC, Gilchrest H, Richard C, Eckel S, Hesk D, West RE et al. Biochemical characterization of desloratadine, a potent antagonist of the human histamine H(1) receptor. Eur J Pharmacol 2002; 449: 229–37.
[21] Gillard M, van der Perren C, Massingham R, Chatelain P. Binding characteristics of $^{[3H]}$levocetirizine to cloned human H1-histamine receptors expressed in CHO cells. Inflamm Res 2002; 51 Suppl 1: S77–S78.