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A comparison of levocetirizine and desloratadine in the histamine-induced wheal and flare response in human skin *in vivo*

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Abstract. *Background:* The histamine-induced wheal and flare response was used to compare quantitatively the antihistaminic potency of levocetirizine and desloratadine.
Methods: In this double-blind, placebo-controlled cross-over study, 24 healthy male non-atopic volunteers received weekly single doses of 1.25, 2.5 or 5 mg levocetirizine, 2.5, 5 or 10 mg desloratadine, or placebo. Four hours after dosing, histamine (100 mg/ml) skin prick tests were performed on the volar surface of both forearms. The diameters of the wheals and flares were measured 10 minutes later. Sedation was evaluated using a visual analogue scale and a motricity test. The effects of individual drug doses were compared using Student's t-test for paired data and the overall effects of the two drugs by ANOVA.
Results: All doses of levocetirizine significantly ($P < 0.0001$) inhibited both wheals and flares in a dose-related manner. Only the 10 mg dose of desloratadine achieved significant inhibition of response. ANOVA showed levocetirizine to be significantly ($P < 0.0001$) more active than desloratadine. Neither drug caused significant sedation or loss of motricity.
Conclusion: Levocetirizine is significantly more effective than desloratadine in inhibiting wheal and flare responses to histamine in human skin *in vivo*, with 1.25 mg levocetirizine being more effective than 10 mg desloratadine.

Key words: Histamine – Skin – Wheal and flare reaction – Desloratadine – Levocetirizine

Introduction

Urticaria, or hives, is a group of closely related conditions largely mediated by mast cell derived histamine. Although some forms of urticaria may have an allergic basis, it is clear that the physical urticarias including dermographism, cold urticaria, solar urticaria, cholinergic urticaria and chronic idiopathic urticaria do not. This is because skin mast cells are able to respond to stimuli other than allergen-IgE interactions. These include stimulation of the complement C5a receptor (CD88) and an activation site for basic neuropeptides, codeine, morphine and compound 48/80, stimuli which release histamine but do not cause the synthesis of prostaglandin D_2 or leukotriene C_4 (1–3]. Also the array of cytokines is much reduced with non-IgE stimulation as evidenced by the absence of a late phase reaction in most forms of urticaria [4].

In urticaria, histamine acting on H_1-receptors, induces local vasodilatation and oedema to cause the wheal and stimulates sensory nerves to cause pruritus and the surrounding neurogenic flare [5]. Thus, it would be expected that H_1-antihistamines should be very effective in relieving the symptoms of urticaria. However, urticaria, and chronic urticaria in particular, are notoriously difficult to treat with antihistamines, high doses of the most potent antihistamines being often necessary to bring symptomatic relief. The main reason for this is the poor diffusion of histamine within the skin, thus allowing it to build up to high local concentrations [5].

As urticaria is largely mediated by histamine, the wheal and flare response to the intradermal injection of histamine is widely used to assess the activity of antihistamines for use in the skin. In this study we have used the histamine-induced wheal and flare response to compare the antihistaminic effectiveness of levocetirizine and desloratadine. Previous studies using single 5 mg doses of each drug [6–8] have shown that levocetirizine had a clear-cut superiority over desloratadine in inhibiting the wheal and flare response to histamine. Consequently, in an attempt to achieve dose-related effects for both drugs and from these calculate equiactive doses, single doses of 1.25, 2.5 and 5 mg of levocetirizine and 2.5, 5 and 10 mg of desloratadine were used.

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Material and Methods

Subjects

Twenty-four healthy male volunteers, 21–57 years old, were recruited half-half in two centres: Sofia, Bulgaria and Cluj-Napoca, Romania. Exclusion criteria involved the presence of skin and allergic disease**,** cardiovascular and other internal organ disorders, alcohol and drug abuse, smoking of more than 15 cigarettes per day. The study was conducted in accordance to ICH-GCP and the local regulations in both countries. The protocol was approved by the local Ethics Review Committees in Sofia and Cluj-Napoca. All subjects eligible for the study signed written informed consent forms.

Study design

This study was a double blind, single-dose, placebo-controlled, seven-way cross-over trial carried out over a period of seven weeks. After an initial enrolment visit, each volunteer was randomly assigned to receive, at weekly intervals, single doses of 1.25, 2.5 or 5 mg of levocetirizine, 2.5, 5 or 10 mg desloratadine or placebo. Commercially available 5 mg tablets of levocetirizine and desloratadine were used in the study, tablets being fragmented for the lower doses. The tablets were cut with a sharp razor and measured on an electronic scale to yield fragments 1/4 or 1/2 of the weight of a whole tablet of levocetirizine, or 1/2 tablet of desloratadine. A single solid fragment of the active drug was always coupled with a corresponding 1/4 or 1/2 tablet of placebo so as not to allow subjects to discriminate between different dosing regimens on the basis of tactile tongue differences between drug and placebo. At 07.00 on the study days, drug doses were swallowed whole with a glass of water with volunteers wearing a mask so as to stay blind to what they were given. The active drug – a whole tablet or a fragment of it – was supplemented by a second tablet or fragment of placebo for all doses other than the 10 mg dose of desloratadine which required the administration of two 5 mg desloratadine tablets. Two tablets of placebo were given on the placebo day. Subjects were not allowed to have breakfast until 15 minutes after drug administration and were not allowed to drink hot beverages, containing caffeine (coffee, tea or coke) or to smoke until after the completion of the study.

Skin prick test

Four hours after drug administration, two skin prick tests were performed with 100 mg/ml histamine, one on the volar surface of each forearm. Ten minutes later, the wheal and flare responses were traced onto acetate sheets and the largest and smallest diameters of each measured. These were then combined to give a single mean value of response.

Sedation

The degree of sedation was assessed by using 100 mm visual analogue scales (VAS). Before the skin prick test, the volunteers were asked to tick the scale as far from its left side ("no sedation whatsoever"), as their subjective estimate of sedation prompted them. The resulting distance was measured in mm and this numerical value used for comparisons of the sedating effects of the different doses of desloratadine and levocetirizine.

Motricity test (deviation from a straight line)

To assess any motor impairment, a motricity test was used in which volunteers were asked to trace over a straight line between two points 10 cm apart. The maximum deviation from a straight line drawn by a ruler for each study dose was then measured and compared with placebo.

Adverse effects

Participants were asked to report any unusual symptoms occurring within the 4 hours following the drug/placebo intake. Before being dismissed they were once again asked specifically about adverse effects.

Statistical analysis

Having demonstrated that the data were normally distributed, parametric statistics were employed for calculating the statistical differences between treatments. Student's t-test for paired data was used to assess the statistical differences between the placebo results and the results of each individual treatment. Because there were a total of 6 treatments, 3 doses of each drug, all dependent on the results of a single placebo group, a significance level of $P < 0.05$ was not stringent enough. Consequently, a Bonferroni correction was used which indicated that $P < 0.01$ to be lowest level of statistical significance under these circumstances. To compare differences within and between treatments i. e. all three doses of levocetirizine and desloratadine as a whole, a two way analysis of variance (ANOVA) was employed.

Results

Wheal and flare results

Histamine triggered wheal and flare reactions in all study subjects.

All doses of levocetirizine significantly ($P < 0.001$) reduced the mean wheal diameter compared with placebo, inhibitions being 31.6, 45.1 and 56.1 % for doses of 1.25, 2.5 and 5 mg respectively (fig. 1a). The effect was linearly dose-related (ANOVA $P < 0.0001$) with an ED_{50} of 3.2 mg. In contrast, doses of 2.5, 5 and 10 mg of desloratadine reduced the mean wheal diameter by only 9.7, 10.1 and 18.4 %, only the effect at the highest dose being significantly ($P < 0.001$) different from placebo. No dose-related activity was found (ANOVA $P = 0.085$). Interestingly, 1.25 mg levocetirizine was significantly ($P = 0.006$) more effective in reducing the wheal response than 10 mg desloratadine.

The inhibition of flare responses followed a similar pattern (fig. 1b), all doses of levocetirizine significantly ($P < 0.001$) reducing the mean flare diameter compared with placebo, inhibitions being 56.9, 61.7 and 73.9 % for doses of 1.25, 2.5 and 5 mg respectively. Again, the effect was linearly dose-related (ANOVA $P < 0.0001$). Doses of 2.5, 5 and 10 mg of desloratadine reduced the mean wheal diameter by 19.7, 13.2 and 31.1 %, none of which significantly different from placebo. Again, no dose-related activity was found with desloratadine (ANOVA $P = 0.261$). As with the wheal, 1.25 mg levocetirizine was significantly ($P < 0.001$) more effective in reducing the flare response than 10 mg desloratadine.

Degree of sedation and motricity test

No statistically significant differences were observed between placebo and the two drugs for either drug with respect to the degree of sedation or the motricity test (table 1). Furthermore, no dose-related effect was seen in either test for either drug.

Discussion

While the EAACI/ARIA guidelines note that histamine-induced wheal and flare studies do not predict clinical efficacy of different antihistamines in allergic rhinitis [9], the extent of blockade of histamine-H_1 receptors in the skin by drug formulations is a close reflection of their potency in urticaria and angioedema, in which histamine plays a leading role [10]. The clinical course of chronic urticaria is rather unpredictable with gross spontaneous fluctuations, which makes the classical clinical designs unreliable. Histamine induced wheal and flare in volunteers is thus regarded as model of urticaria and can be used to objectively compare in a double blind placebo controlled crossover fashion preparations used for treatment of these disorders. This approach is all the more important bearing in mind that many difficult to treat cases of urticaria would warrant stepping up the antihistamine treatment well above the registered doses. It is conceivable that using the most potent H_1-antihistamines as determined by such trials would yield the highest chances for optimal effective dose treatment.

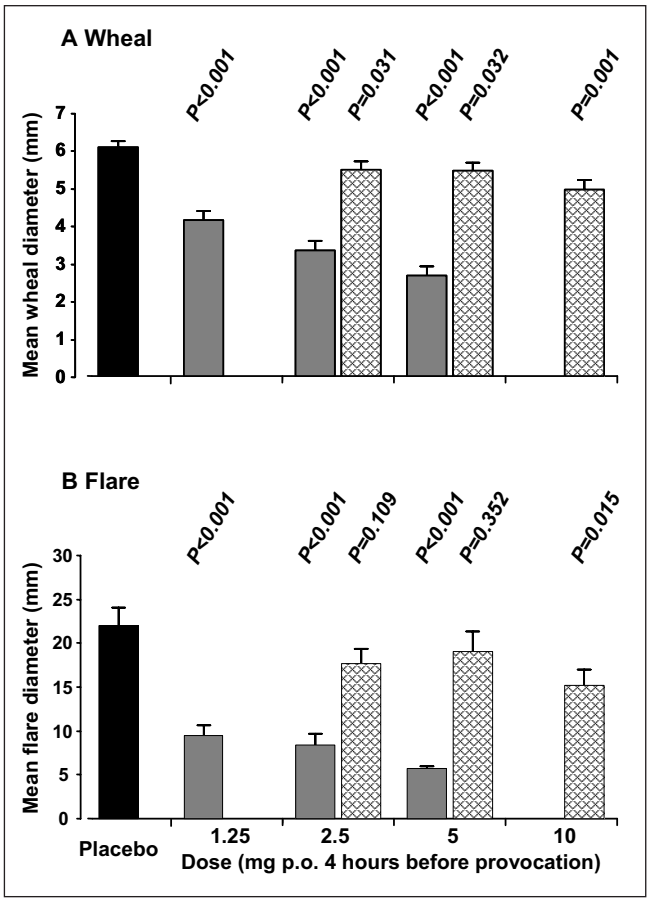

Figure 1. The effect of levocetirizine and desloratadine on the histamine-induced wheal and flare response. Responses were provoked by skin pricks with histamine (100 mg/ml) four hours after administration of drug or placebo. Wheal and flare diameters were measured 10 minutes later. Each result is expressed as the mean ± standard error of the mean result for 24 volunteers. The significance of differences from placebo was calculated by Student s t test for paired data. As multiple tests were made against a single value of placebo, a Bonferroni correction indicated P = 0.01 to be the minimum level of statistical significance. Black bars indicate placebo, grey bars levocetirizine and hatched bars desloratadine.

Our data confirm previous reports using single 5 mg doses of each drug [6–8] that levocetirizine had a clear-cut superiority over desloratadine in inhibiting the wheal and flare response to histamine. Statistically significant reductions of wheal reaction versus placebo were observed with all three doses of levocetirizine, but only with the highest dose (10 mg) of desloratadine. Even this last reduction was smaller than the reduction obtained with the lowest dose of levocetirizine. This result was paralleled for the flare reaction in which all doses levocetirizine exceeded 50 % inhibition and were highly significant while no dose of desloratadine significantly reduced the flare. The greater sensitivity of the flare to inhibition by antihistamines concurs with the report that while both H_1- and H_2-receptors are involved in the wheal response, H_1-receptors were primarily responsible for the flare and itch [11].

The reason for the difference in activity between the two drugs is likely to be explained by their different pharmacological profiles. Although desloratadine has an almost 10-fold stronger binding affinity than levocetirizine (0.4 nM versus 3 nM) [12, 13], it has a much greater volume of distribution [14] and, hence, a lower extracellular concentration. This has been confirmed by the reports that the concentration of free desloratadine in the plasma four hours after administration is almost 30 times lower than that of levocetirizine (1 nM versus 28 nM) [15, 16]. From these data, Gillard and colleagues have calculated the theoretical percentage receptor occupancy of histamine H_1-receptors at four hours to be 90 % for levocetirizine and 71 % for desloratadine thus predicting levocetirizine to be the more active in the *in vivo* situation [16].

Table 1. Degree of sedation and deviation from straight line (DSL)

	PLA	LC 1.25 mg	LC 2.5 mg	LC 5 mg	DL 2.5 mg	DL 5.0 mg	DL 10 mg
Sedation (mm)	5.83 ± 1.60	7.46 ± 2.11	10.9 ± 3.05	7.83 ± 2.87	5.79 ± 1.58	5.5 ± 1.13	8.46 ± 2.26
DSL (mm)	1.94 ± 0.19	1.9 ± 0.21	2.08 ± 0.26	1.92 ± 0.21	1.52 ± 0.14	2.27 ± 0.22	1.56 ± 0.15

The degree of sedation was assessed four hours after drug administration by using 100 mm visual analogue scales (VAS) ranging from no sedation whatsoever to very heavily sedated . In the motricity test (deviation from a straight line) volunteers were asked to trace over a straight line between two points 10 cm apart. The maximum deviation from a straight line drawn by a ruler for each study dose was then measured and compared with placebo. Each result is expressed as the mean ± standard error of the mean result for 24 volunteers. PLA = placebo; LC = levocetirizine; DL = desloratadine.

Side effects could be a major hurdle if higher doses of drug were to be used in difficult cases of urticaria. Concerning sedation and performance impairment, we did not observe any statistically significant effects with either drug confirming previous studies focusing on sedation and performance impairment. Two studies demonstrated that desloratadine and levocetirizine did not alter driving performance, compared to diphenhydramine (a first generation antihistamine) [17, 18]. Also, levocetirizine did not impair memory and attention after acute and chronic administration [19].

In conclusion, levocetirizine is much more effective than desloratadine in inhibiting histamine-induced wheal and flare responses in healthy male volunteers at non-sedative doses of both drugs. The clinical significance of these data is especially relevant to working out novel schemes for urticaria treatment.

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