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DIFFERENCES IN THE HISTAMINE-INDUCED WEAL AND FLARE INHIBITION BETWEEN CETIRIZINE AND LORATADINE

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Summary

Background: Different studies demonstrate superiority of Cetirizine over Loratadine in the suppression of flare reactions caused by Epicutaneus Skin Prick Test with Histamine (ESPTH) but there are contradictory evidences regarding their effect on the weal reactions. This study aimed to compare these superiorities.

Method: Loratadine 10 mg and Cetirizine 10 mg were given to 26 volunteers in a double-blind, randomized cross-over method. The subjects performed the ESPTH immediately before the medications were administered, and then 30 minutes, 1, 3, 5, 6 and 24 hours after they received the drugs. Twenty minutes after each ESPTH, flare and weal were drawn into a transparent paper. After four weeks the subgroups changed the drugs and underwent the same procedure.

To analyze the differences between flare and weal, we carefully cut the transparent paper tracings and weighed them in an analytical weighing-machine. The differences were analyzed with Wilcoxon Signed Ranks Test.

Results: Cetirizine was more effective on inhibiting the flare (at 3, 5, 8 and 24 h post-dosing) and the weal (at 3, 5 and 8 h post-dosing) than Loratadine ($p<0.05$). This superiority (difference) was greater on the flare than on the weal, especially at the measurements performed at 3, 5, and 24 hours after the antihistamine administration ($p<0.05$).

Conclusion: Cetirizine and Loratadine may have differences in the way they exert their antihistaminic effect. At least one of the antihistamines may have an additional mechanism, other than the inhibition of H1, that influences the weal or/and the flare caused by ESPTH.

Keywords: Cetirizine, Loratadine, histamine, histamine H_1 antagonists, skin tests.

Introduction

Cetirizine and loratadine, two second generation antiH1$_s$ known to act as inverse agonists [1], have a pharmacological effect of about 24 hours with lesser adverse effects than first generation antiH1$_s$ [2]. They are extensively used to prevent the symptoms of allergies, especially in the skin, eye, and nose, superseding their first generation predecessors [2].

The skin tests with histamine (H) are often used to evaluate and compare effectiveness of antihistamines in humans, as well as their differences in onset and duration of action. While different studies clearly revealed superiority of C (Cetirizine) over L (Loratadine) in the cutaneous histamine-induced flare reaction [3, 4] this cannot be seen in the inhibition of the histamine-induced weal reaction where the three possible situations can occur [3–6].

The aim of our study was to compare and analyze the differences in the weal and flare inhibition between Cetirizine and Loratadine.

Methods

Materials

In this study we used tablets of 10 mg, of C and L produced from the same company (Dr. Reddy's Laboratories). This was a double-blind study in which only the principal investigators knew which volunteers received which medication. The principal investigator prior to administration crushed the tablets, which were then reformulated into identical capsules.

For the ESPT we used a histamine solution with a concentration of 1.7 mg/ml containing glycerol, NaCl and phenol (Allergopharma Joachim Ganzer KG), and single-use metallic lancets.

The transparent paper used to trace weal and flare responses had a specific weight of about 9.36±0.02 mg/cm^2. The possible calculated error due to the paper weight heterogeneity was 0.2 mm^2 per cm^2. All the entire above-mentioned test items were obtained from commercial sources.

For paper weighting we used an analytical balance (model OHAUS Analytical Standard, Model AS60S), which weighs out until 0.1mg (converted in paper surface, 1.1 mm^2). The maximal error due to the paper heterogeneity and the weighting machine was 1.3 mm^2 per cm^2.

Subjects

Twenty-six healthy volunteers, 13 of which were males, were recruited for this study. They have a mean age of about 21.8±2.6 years with a maximum and minimum age respectively 32 and 20 years. Their body heights ranged 161 to 183 cm with a body weight 52 to 81 kg. A detailed medical history and examination, including a panel for liver and renal function, were used to confirm their healthy state. The laboratory tests were repeated after the study.

Exclusion criteria included any medicine used within one week, history of specific drug hypersensitivity or intolerance (loratadine, cetirizine, any medicine chemically related to them, their excipients or other substances), clinically evident allergic disease, other chronic, acute or passed diseases (cardiovascular, gastrointestinal, hepatic, renal, allergic, respiratory, endocrinological, neurological, or psychiatric disease) and the use of stimulants.

The research followed the ethical standards formulated in the Helsinki Declaration of 1964, revised in 2000, and was approved by the National Bioethical Committee. Everyone signed an informed consent for the participation and was free to withdraw from the study at any time and for any reason. At the same time, the investigator could also exclude any volunteer for reasons of safety or protocol deviation that could depreciate the interpretation of the results.

Study design

This was a double-blind, one-dose, randomized cross-over, experimental study on healthy volunteers. It was approved by the National Comity of Bioethics.

The volunteers were randomly divided in two subgroups. They received 10 mg of L and 10 mg of C respectively according to the double blind method (one capsule of either cetirizine or loratadine, identical in appearance) at 07:00 a.m. along with 200 ml of water, after overnight fasting. The volunteers abstained from caffeine, alcohols and fruit juices 12 hours before the experiment and for the 24-h evaluation period afterward. Plain water drinking and eating were allowed four hours after they had received the drugs. Treatment periods were separated by a four week wash-out interval.

Skin prick test

The main outcome variable was the weal and flare response to the ESPTH challenge. We conducted the skin prick in the forearm of each volunteer on seven occasions (pre-dose and ½, 1, 3, 5, 6, and 24 h post-dosing), by placing a droplet of H solution on an untested part of the forearm and then piercing the skin with the lancet. An Epicutaneus Skin Prick Test with distilled water (negative control) was performed at the same time with the first ESPTH. Twenty minutes after each skin prick test, flare and weal were drawn into a transparent paper. All ESPTH and measurements were made by the same person.

Assessment Criteria

We cut the flare and weal tracings and weighted them with an analytical balance. The weights were converted in surfaces and the values were expressed in percentage of the initial values. We considered a total inhibition of flare or weal area when the surface was <2mm^2.

We assessed the antihistamine activity by the post-dosing changes in the histamine-induced weal and flare areas expressed as follow:

Direct parameters: Negative control flare area (cm^2) = Ncfa, Negative control weal area (cm^2) = Ncwa, Histamine flare area (cm^2) = Hfa, Histamine weal area (cm^2) = Hwa.

Derived parameters: As the negative control flare and weal areas were 0, the respective negative control adjusted areas at different time points were equal to the respective histamine flare and weal areas.

Percent change from baseline of adjusted flare area at time *t* (%) $=(Hfa_t–Hfa_o)*100/Hfa_o$

where Hfa_t and Hfa_o were histamine flare areas at time points *t* and *o* respectively.

Percent change from baseline of adjusted weal area at time t (%)$=(Hwa_t–Hwa_o)*100/Hwa_o$

where Hwa_t and Hwa_o were histamine weal areas at time points *t* and *o* respectively.

SFI (Superiority on flare inhibition) $=[(Hfa_t–Hfa_o)*100/Hfa_o]_C–[(Hfa_t–Hfa_o)*100/Hfa_o]_L$

SFI-TR (SFI-Trend Removed) $=[(Hfa_t–Hfa_{prev})*100/Hfa_{prev}]_C–[(Hfa_t–Hfa_{prev})*100/Hfa_{prev}]_L$

SWI (Superiority on weal inhibition) $=[(Hwa_t–Hwa_o)*100/Hwa_o]_C–[(Hwa_t–Hwa_o)*100/Hwa_o]_L$

SWI-TR (SWI-Trend Removed) $=[(Hwa_t–Hwa_{prev})*100/Hwa_{prev}]_C–[(Hwa_t–Hwa_{prev})*100/Hwa_{prev}]_L$

where Hfa_{prev} and Hwa_{prev} were respectively histamine flare and weal areas of the previous time point.

During the experiment we recorded all adverse clinical phenomena reported from the volunteers and observed from the investigators.

Statistical analysis

The distribution of the inhibition data were tested with the Shapiro-Wilk Test. As almost all the inhibition data were not normally distributed and could not be appropriately transformed, they were analyzed with nonparametric methods. The differences were analyzed with Wilcoxon Signed Ranks Test. The categorical data were analyzed with Fisher's Exact Test. All the statistical tests were two-sided with significance of 5%. The total weal and flare surface areas were estimated as the area under the curve (AUC) between the baseline and

the individual area time curves, from 0 to 24 h after drug intake, by the trapezoidal rule, and expressed as mm^2min^{-1}.

Results

None of the volunteers withdrew or were excluded by the investigator during the experiment.

No flare or weal was observed after the ESPT with negative control in any of the volunteers.

Weal

No difference was observed in the weal area between the two subgroups before the antihistamine administration. Cetirizine and Loratadine both significantly inhibited the ESPTH weal ($p<0.02$ vs. ESPTH weal before the antihistamine administration) from 30 minutes up to 24 hours post-dosing. Cetirizine had a stronger effect on ESPTH weal inhibition at 3, 5 and 8 h post-dosing ($p<0.05$; vs. Loratadine) (*Figure 1*). The median $AUC_{(0-24h)}$ of the Weal for L was 1436 mm^2 and for C 954 mm^2 ($p<0.05$) (*Figure 2*). Cetirizine gave a weal inhibition over 90% in 3 (12%) subjects while Loratadine in no one (0%) subject.

see Fig. 1

Flare

No difference was observed in the flare area between the two subgroups before the antihistamine administration. Cetirizine and Loratadine significantly inhibited the ESPTH flare ($p<0.05$ vs. ESPTH flare before the drug administration), from 30 minutes up to 24 hours after dosing. Cetirizine showed a stronger inhibition over Loratadine during all the ESPTH, but this begins to be statistically significant at three hour post-dosing and continues to be statistically significant even 24 h post-dosing ($p<0.05$), (*Figure 1*). The median $AUC_{(0-24h)}$ of the Flare for L was 9300 mm^2 and for C, 4428 mm^2 ($p<0.05$) (*Figure 2*). Cetirizine gave a flare inhibition over 90% in 17 (65%) subjects and Loratadine in 6 (23%) subjects.

Cetirizine superiority on ESPTH flare inhibition (SFI) was greater than in the weal inhibition (SWI) at 3 h ($p=0.02$), 5 h ($p=0.37$) and 24 h ($p=0.048$) post-dosing, but this was evident only at 3 h post-dosing when comparing the SFI-TR vs. SWI-TR ($p=0.042$). No statistically significant differences were observed between the SFI and SWI at 30', 1 h, and 8 h post dosing.

see Fig. 2

Safety

Four subjects reported 'moderate fatigue' after they received Cetirizine and only one after Loratadine. None reported 'somnolence'. No deviation from normal laboratory test was observed after the study termination.

Discussion

The subjects did not suffer from any allergic disease and the ESPTH reflects predominately the histamine effects on the skin. Meanwhile, the ability of the H_1-antagonists to inhibit the weal and flare reaction is a well-documented fact and the skin prick test with histamine is a reliable method for measuring their antihistamine antagonism [7–9]. The cross-over design ensures a within-subject comparison and the four weeks wash-out time period is sufficient to prevent the carry-over effect. This study design seems adequately accurate to compare their time of onset and duration of action as their relative efficacy.

Our study shows that C and L significantly inhibited the skin reactivity to H through 24 hours at therapeutic dosage, 10 mg each. At the same time, it clearly manifested the superiority of cetirizine over loratadine both in the ESPTH flare and weal inhibition which, is in concordance with other studies (*Figure 1*, *Figure 2*) [10–13]. The number of subjects that experienced an ESPTH flare inhibition ≥'3d90% was significantly higher after C administration compared to the one after L administration ($p=0.01$), in contrast to the ESPTH weal inhibition.

Cetirizine relative superiority on ESPTH flare inhibition was greater than in the ESPTH weal inhibition at three post-dosing measurements (3, 5, and 24 h). After a trend-removed analysis this superiority was confirmed only at 3 h post-dosing, which revealed that the differences at 5 and 24 h would have been influenced by what happened prior to the 3 h post-dosing measurement.

C and L may have differences in the way they exert their antihistaminic effect. At least one of the antihistaminics may have an additional mechanism, other than the inhibition of H_1, that influences the weal or/and the flare caused by ESPTH.

As it was observed that H_1 antagonism alone achieves only 85-90% of the inhibition of H induced weal and flare reaction, the H_2 receptor involvement is suggested in vascular response to H in skin [14–17].

Although there are no data about the flare/weal proportionality of action of histamine through H_2 receptors, the odds are that this is different from its action through H_1 receptors. It is believed that the histamine weal is caused by contribution of both H_1 and H_2 receptor [18, 19] and the flare mainly by the H_1 receptors [15].

At the same time some authors evidenced little effect of H_2 receptor antagonists on the weal inhibition [20]. In another study cimetidine inhibited both skin weal and flare caused by H, but when it was combined with chlorpheniramine it added its inhibition effect only on the flare [21]. Both C, L, and their main metabolites have a high H_1 receptor selectivity [22, 23]. The above data by all odds may exclude the possibility that any of the drugs tested on our study may exert additional direct effects through H_2 receptor inhibition. But this conclusion cannot be definitive as we do not know enough details for all the metabolites of C and L. The situation becomes more entangled if we consider the suggested role of H_3 receptors in vasodilatation [24].

The most potent action of H through receptors is involved in the flare response, whereas there are more inflammatory mediators involved on the weal formation, especially in the skin tests with allergen [25]. Some of these mediators may confound the interpretation of histaminergic response even in the ESPTH as they may be the product of the trauma caused by the test [26, 27]. Meanwhile the action of histamine on H_1 receptors induces the production of inflammatory products such as the nitric oxide and prostacycline [28].

At the same time now it is a well-known fact that both C and L have other anti-inflammatory effects not mediated by H_1 receptor [29–33] even at therapeutic concentrations [34] which may be the reason for these discordances of flare and weal inhibition by these two antihistamines. Therefore, a comparison of these two antihistamines with a non-invasive method of histamine application like the iontophoresis may clarify much more about this situation.

As the differences in histamine weal suppression are not so "evident" between C and L, which correspond to the differences in clinical effect of most of the studies on chronic idiopathic urticarial, seasonal allergic rhinitis and atopic dermatitis [35–37], we may suggest here that these are more predictive to the last one when compared to the respective differences on flare inhibition.

The study of the mechanisms of weal formation in ESPTH and the causes of differences such as these between L and C may help to better characterize the clinical impact of these differences on allergic diseases.

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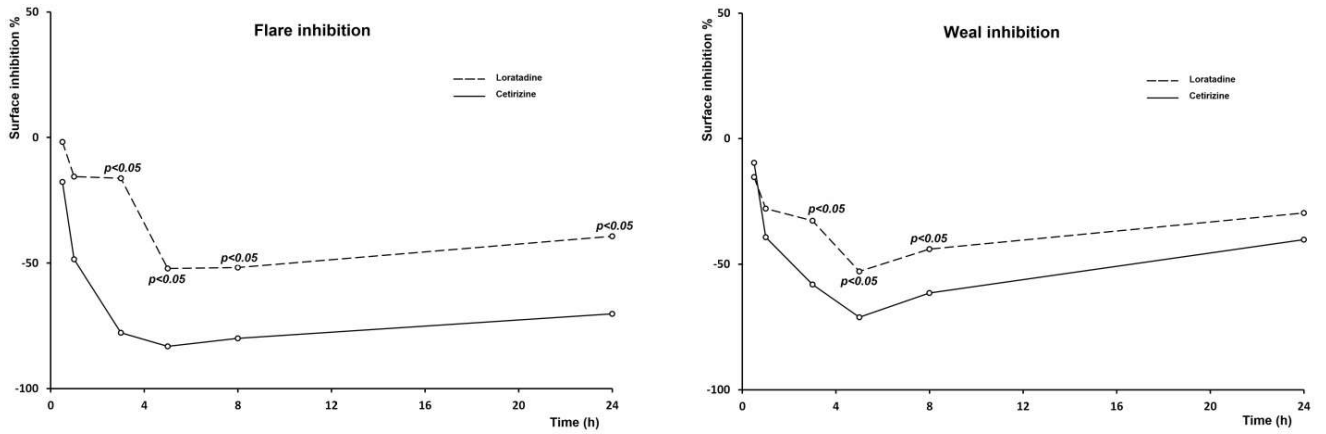

Fig. 1: Median percentages of Weal and Flare inhibition by Cetirizine and Loratadine after Epicutaneus Skin Prick Test with Histamine.

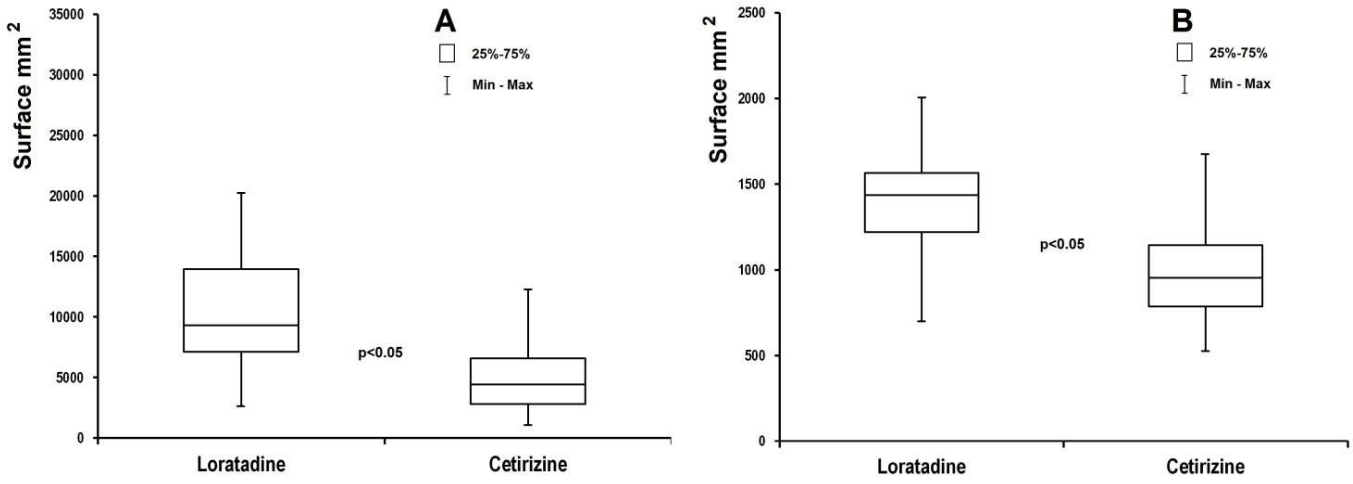

Fig. 2: Global Flare (A) and Weal (B) areas under the curve 0-24h (median, 1st and 3rd quartiles, maximum and minimum values). Both differences are significant (p<0.05).