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Antiinflammatory Properties of Cetirizine in a Human Contact Dermatitis Model

Clinical Evaluation of Patch Tests Is Not Hampered by Antihistamines

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The aim of this double-blind, placebo-controlled, randomized, cross-over pilot study was to assess the antiinflammatory properties of cetirizine. A group of 27 patients with a positive patch test to an allergen consecutively received cetirizine 10 mg o.d. or placebo during a 14-day period, respectively. At day 11 of each period, patch testing was performed with the allergen. The image analysis showed a skin reaction significantly reduced under cetirizine ($p=0.03$), but the clinical recording and the standardized chromatometry did not show any difference between groups. In the cross-over analysis the results of image analysis were influenced by the period, but this effect disappeared after adjustment of the ambient temperature during the 3 days of the test. These results demonstrate that cetirizine has an impact on the inflammatory process in a clinical model of cell-mediated allergic reaction, although this effect is only detected with a very sensitive technique. They also show that it is useless to stop antihistamines before patch testing, since clinical evaluation of tests is not hampered by a potent antihistamine. Additionally this study suggests that ambient temperature has an influence on the results of tests. **Key word:** *delayed-type hypersensitivity*.

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Cetirizine is a potent antihistamine H1 (1), which displays interesting antiallergic and antiinflammatory properties (2). Ten mg cetirizine inhibits the migration of eosinophils (3) induced by an allergen in atopic patients. Cetirizine also inhibits the migration of neutrophils and basophils in the late phase cutaneous reaction after an allergenic challenge (4). Recent data suggest that cetirizine interferes with the expression of adhesion molecules (5).

Antihistamines are useful in the treatment of immediate skin reactivity observed in urticaria. Although there is no clear demonstration of their activity on the delayed type of skin reactions, antihistamines are often proposed in atopic dermatitis or contact dermatitis as an adjuvant to topical steroids.

Beside its antihistamine H1 effects, the antiinflammatory effects of cetirizine may provide a rationale for an activity in eczema. Contact dermatitis is a model of delayed-type hypersensitivity which makes it possible to test this hypothesis. A study was designed to evaluate the effect of a prolonged

treatment with cetirizine on the reaction to a contact allergen applied by patch testing in a sensitized population.

METHODS

Design

The aim of this double-blind, placebo-controlled, randomized, cross-over pilot study was to evaluate the impact of cetirizine 10 mg o.d. on the development of contact dermatitis. Patients known to be sensitized to a contact allergen were randomly assigned to receive successively 10 mg cetirizine o.d. or placebo during a 14-day period and the opposite during the next 14 days. At day 11 of each period patch testing was performed with the previously recognized allergen according to the guidelines of the International Contact Dermatitis Research Group (ICDRG) (6). This test was read 72 h later (7) at day 14 of each period. Observance was controlled by count of the remaining treatment after the 14-day treatment period.

Patients

Patients were recruited from the test laboratory of our department from patients consulting for contact dermatitis. To be included they had to have at least one positive test with an allergen from the ICDRG list (8), graded from + to +++ at 72 h according to the ICDRG scale (6). They were enrolled after they had given written informed consent. Exclusion criteria were the following: more than 3 positive patch tests on the ICDRG list (risk of polysensitization), atopic patients according to clinical history (absence of asthma, allergic rhinitis or conjunctivitis and atopic dermatitis), patients with an eczema in the back (no possibility of testing), patients with a severe organ deficiency, patient under treatment with ketotifen in the 2 weeks before the trial, astemizole in the last 6 weeks, other antihistamines or topical corticosteroids in the last week, or systemic corticosteroid in the last 2 months, and patients allergic to cetirizine, piperazine and other components of cetirizine pills.

Patch testing

Tests were performed according to the ICDRG guidelines (6), using one of the allergens. When the patient had 2 or 3 positive tests, the allergen which had given an intermediate reaction (++) was chosen (exclusion of extreme reactions, + and +++).

Assessment of the tests

The skin reaction was evaluated on day 14 of each period using the ICDRG clinical recording of tests, an analogic scale of pruritus and by means of colour quantitation using chromatometry and image analysis. The tests were performed in all patients on the same date. The measures were achieved under standardized conditions of temperature $21 \pm 1^\circ\text{C}$, after 72 h, 1 h after the patch had been removed.

Clinical assessment of the intensity of the reaction was carried out according to the recording system of ICDRG (7): – negative, ?+ doubtful reaction (faint erythema), + weak positive (erythema, infiltration, possibly papules), ++ strong positive reaction (erythema, infiltration, papules, vesicles), +++ extreme positive reaction

(intense erythema, infiltration, coalescing vesicles). The ? + to +++ system was converted into numeric values (0, 1, 2, 3, 4) for statistic evaluation. Pruritus was evaluated on a non-graduated analogic visual scale with 2 extremities: 0=no pruritus, and 100=maximum imaginable pruritus. The reaction to patch tests was also assessed by means of chromatometry and image analysis.

The reflected-light colour of the skin was measured using a tristimulus reflectance meter (Chromameter Minolta CR 200, Japan). The measurement was based on the standard L*, a*, b* colour system as recommended by the "Commission Internationale d'Eclairage 1976". Luminance (L*) represents the relative brightness ranging from total black value to pure white, b* the colour ranging from blue to yellow. The red-green component involved in skin erythema is expressed by a*, ranging from -100 (green) to +100 (red). To quantify the erythema due to the skin test, the light reflected from skin test-irradiated with white light was analyzed in the green and red range (a*). This light was converted into a numeric value according to the norms of the "Commission Internationale de l'Eclairage" after the Chromameter had been calibrated to a standard white plate.

Finally the patch test reaction was assessed using image analysis (9). Colour slides of the tests were obtained under the same standardized conditions of temperature, using a camera Nikon F 301 with a 105 mm focal length lens and a Kodachrome 64 ASA professional. They were processed at the same time in the same laboratory, digitalized and stored on a Kodak CD. The images were recorded on RGB (red, green and blue) frames. Surface of erythema was expressed as a number of pixels.

Tolerance

Tolerance of the drug was assessed by an open questionnaire at the end of each period of treatment.

Statistics

Treatment effect and period effect were assessed using a non-parametric 2 period-change analysis, as described by Koch (10).

RESULTS

Patients and treatment

Twenty-five females and 2 males with a median age of 34.5 (min. 20, max. 66) were enrolled in the trial on the basis of

their patch test, after having given their informed consent. The patients were randomized either to the sequence cetirizine-placebo or to the sequence placebo-cetirizine. Mean age was 31.8 in the first group and 39 in the second ($p < 0.05$). The two groups were comparable as to sex and weight, weight/size ratio, medical history, duration of contact dermatitis, and intensity of the initial test on the ICDRG scale. The selected allergen was nickel in the 27 patients, accounting for the male to female ratio in this trial. One patient did not complete her treatment at the end of the first period. She was kept in the intend-to-treat analysis.

Patch tests

The intensity of the patch test reaction, as assessed by clinical evaluation with the ICDRG recording system, pruritus scale and chromatometry, was not significantly different in placebo- and cetirizine-treated patients, using comparison of paired series or cross-over analysis (Table I). Analysis did not show any difference between the periods (placebo first vs. cetirizine first). With the use of image analysis (Table I), there was a significant decrease in the erythema of patch tests under cetirizine, as compared to tests under placebo ($p = 0.04$). This was also significant in the 26 patients who completed the treatment. The erythema measured by image analysis was also significantly higher ($p = 0.04$) in the second period of treatment (day 28) than in the first (day 14) (Table I), regardless of those who had cetirizine or placebo first, thus suggesting that it was neither an individual effect nor a therapeutic effect but a period effect. As the conditions for obtaining images were standardized and identical in both test periods, we looked for an environmental factor which could have been different in the two periods but identical for all patients. A climatic change between the first and the second period was suspected. The temperature recorded by National Meteorology records displayed a clear-cut difference of 4°C between the mean temperature during the 3 days before the first period of treatment and the 3 days before the second. After standardization of the

Table I. Comparison of tests under placebo and cetirizine

Measurement of the test	Placebo mean median m1/m2	Cetirizine mean median m1/m2	<i>p</i> Treatment effect	<i>p</i> Period effect
Clinical evaluation ^a	3.3 ± 0.9 3.0 3.3/3.4 (1/3/11/10/2)†	3.1 ± 0.9 3.0 3.0/3.2 (1/6/10/10/0)†	0.68	0.20
Chromatometry ^b	14.69 ± 3.24 14.11 14.58/14.80	14.14 ± 3.89 14.35 13.98/14.32	0.47	0.81
Image analysis ^c	51.07 ± 25.15 51.31 47.22/54.65	41.73 ± 19.07 35.19 36.71/48.22	0.03	0.02
Pruritus ^d	28.9 ± 26.4 22.0	30.1 ± 26.4 25.0	0.59	0.92

m1 and m2 = mean of the values of the test at the end of the first period (m1) and of the second period (m2) in the cross-over study.

^a 0 to 4 numeric values correspond to -, +?, +, ++, +++ as described by ICDRG (see methods).

^b Numeric value for a* according to "Commission Internationale d'Eclairage 1976" (see methods).

^c Surface of erythema in pixel × 10³ (see methods).

^d mm on a 10-mm analogic scale (see methods).

† Distribution of patients from - to +++ for the ICDRG.

surface of erythema measured by image analysis to the mean of the temperature during the 3 days before reading the test, the values were still significantly lower in cetirizine-treated patients than in controls ($p=0.017$), but the period effect was no longer significant ($p=0.53$).

DISCUSSION

Therapeutic trials in contact dermatitis or atopic dermatitis are often difficult to conduct and to interpret. This is due to a number of confounding factors such as the natural evolution of the disease, the difficulty of identifying and controlling responsible allergens, or to drawbacks such as the difficulty of using placebo when the pruritus and the eczema are intense. Patch testing provides a simple and efficient model to test the efficacy of drugs in delayed-type hypersensitivity in humans. Once a contact allergen is identified by patch testing in a given individual, the skin reactions to a standardized patch test with and without treatment can be compared. Only nickel-allergic patients were included in this study. Nickel has been shown to be one of the most reproducible patch test allergens when a patient is rechallenged (11). Therefore, nickel allergy is probably a robust and reliable model to assess the effect of a drug. Testing cetirizine in this model showed a clear effect on the results of the patch test, although this was not clinically detectable by the usual visual reading.

The results of this study provide useful data on cetirizine activity. This is the first in vivo study showing that cetirizine has an effect on the inflammatory process in a clinical model of cell-mediated allergic reaction. Although this effect is only detectable with the use of a very sensitive technique such as erythema quantitation by image analysis, these data show that cetirizine can decrease the skin reaction due to a delayed type of hypersensitivity, in which histamine plays a minor role, if any. These data confirm the complex antiallergic activity of this drug, which is not limited to IgE-mediated processes. This effect is likely to be due to the antiinflammatory properties of cetirizine, such as its effects on eosinophils, neutrophils and basophils (2) rather than to its antihistamine activity.

The therapeutic effect of 10 mg cetirizine on contact dermatitis is likely to be weak, since the impact was detected by image analysis and not by clinical score. Higher doses of cetirizine, which may potentiate the effect, may be worth evaluation. However, the absence of a detectable effect of a cetirizine when the ICDRG reporting system is used does not rule out a clinical effect, since clinical scoring of patch tests probably has a very low sensitivity to therapeutic changes. Indeed, even cyclosporine, which has a potent clinical impact on eczema, does not seem to modify the clinical score of intense reactions to contact allergens in patch tests (12).

This trial also provides us with two important data in the field of clinical dermatology: patch testing under antihistamines and standardization of patch tests. Whether or not treatments must be stopped before testing is still a matter of debate. Comparison of intensity of reaction before and during treatment with corticosteroids has suggested that an important allergy cannot be missed under corticosteroids up to 20 mg (13–15). However, it is usually advisable to defer the test after corticosteroids have been stopped. As to antihistamines, there is considerable uncertainty (6). Feuerman & Levy (14) did not find any difference in the patch reaction after mebhydrolin napadisylate. Lembo et al. (16) reported

that cinnarizine, an antihistamine with other antiinflammatory effects, reduced the patch test reaction in 5 of 17 patients, but these results were obtained in an open study without controls. Dermatologists usually feel uncomfortable testing patients under treatment with antihistamines and prefer to delay testing until antihistamines have been stopped. The results of our double-blind cross-over controlled study show that the clinical reading of a patch test is not hampered by one of the most potent new antihistamines. Although our results were obtained in contact allergy to nickel, they can probably be generalized to other allergens. Therefore, stopping antihistamines or delaying testing in patients under antihistamine treatment is useless. This may facilitate patient testing in daily practice.

Another unexpected practical piece of information was provided by this study. The cross-over analysis of the results of image analysis showed a period effect (Table I). A similar trend, although not significant, was detected on chromatometry. This effect can neither be due to treatment nor to the conditions of the measures. A clear-cut increase ($+4^{\circ}\text{C}$) in ambient temperature occurred between the two 3-day periods of the tests. After standardization, there was no longer a difference between the two periods, whereas the effect of treatment remained significant. These data suggest that ambient temperature during the test period, or another factor closely correlated to ambient temperature, may influence the results of patch testing. A higher ambient temperature may increase penetration of allergens by inducing sweating or facilitate inflammation by vasodilatation or enhance irritating effect by sweating under occlusion. Although this effect on tests of a 4°C change in ambient temperature was only detected by image analysis, we may suppose that the seasons or the life habits (clothing, heating etc.) could explain some differences in the results of patch testing. This effect would deserve further investigation, since it could be a limit to the necessary standardization of tests.

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