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Short communication

Duration of the antihistaminic effect after discontinuation of ebastine

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Background: The inhibitory effect of antihistamines on allergen-induced skin reactions can impair the results of allergen skin testing, which are necessary for the diagnosis of atopic diseases. This study was designed to determine the time period required for the inhibitory effect of ebastine on allergen-induced skin reactivity to disappear completely.
Methods: This was a double-blind, placebo-controlled, parallel-group study including 23 out of 27 randomized patients. They received either ebastine 20 mg or placebo once daily for 7 days. At the end of treatment, allergen challenge was performed daily for 7 days. Histamine challenge was performed on day 1 (6 and 24 h) and day 5 after treatment. The wheal and flare surface areas were measured and analyzed.
Results: Highly significant inhibition of the wheal and flare response induced by allergen was observed after ebastine treatment on days 1 and 2 as compared with placebo ($P<0.01$ for both). The inhibition was reduced, although still significant, by day 3 ($P<0.05$). No significant difference was observed by day 4 between the ebastine and the placebo groups. The effects of histamine challenge were significantly reduced in the ebastine compared with the placebo group at day 1 (6 and 24 h), and were similar at day 5 after treatment.
Conclusions: Our results show that the wheal and flare response to allergen after ebastine discontinuation returns to placebo values after 4 days. Therefore, patients using ebastine need to be antihistamine-free for 4 days before the skin prick test. This is valuable information for the allergologist seeking to diagnose allergen sensitivity.

Key words: allergy; antihistamine; ebastine; histamine challenge; skin prick test.

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Vast arrays of histamine-blocking agents are currently available for the treatment of medical conditions such as seasonal and perennial allergic rhinitis, urticaria, and other allergic disorders. The second-generation antihistamines, including astemizole, azelastine, cetirizine, loratadine, terfenadine, fexofenadine, ebastine, and mizolastine, appear to possess good antiallergic properties, with low or no sedative effects, and no anticholinergic activity at therapeutic doses (for reviews, see Refs. 1–3).

Ebastine, one of the newest of the second-generation agents, is a long-acting, once-daily antihistamine (4). It has been shown to be effective in seasonal (4–9) and perennial allergic rhinitis (10–12). The antihistaminic effect of ebastine has been found, by histamine challenge testing of skin reactivity, to inhibit the wheal and flare response induced by histamine at 4 h (13, 14) for up to 24 h (15, 16).

The inhibitory effect of antihistamines on skin reactions can complicate the results of skin testing with allergens, which is routinely used for the diagnosis of atopic diseases. In order to eliminate antihistamine interference in skin test results, it is necessary to determine the duration of effect for each agent, thus allowing the drug to be discontinued for an appropriate period of time prior to the test. This study was designed to determine the time period required for the disappearance of the inhibitory effect of ebastine, when administered 20 mg/day, on the skin's reactivity to an allergen to which the patient is sensitized, as compared to placebo.

Material and methods

This was a randomized, double-blind, placebo-controlled, parallel-group study conducted at a single center (ART, Centre Hospitalier Lyon Sud). The protocol was approved by the institutional ethics committee, and all subjects provided written, informed consent.

Patients

Twenty-three out of 27 randomized patients were included in the per-protocol population for efficacy analyses (12 in the ebastine group and 11 in the placebo group). All patients received at least one dose of test medication (14 in the ebastine group and 13 in the placebo group), and were included in the analyses of adverse events (Table 1). The sample size was calculated to demonstrate a 25% one-sided equivalence of ebastine 20 mg to placebo with $\alpha = 0.05$. Eligible patients were between the ages of 18 and 50 years, with at least a 1-year history of symptomatic atopy, rhinitis, and/or conjunctivitis with or without asthma, due to sensitivity to a well-defined allergen (grass pollen, birch pollen, house-dust mite, and cat dander).

Inclusion criteria were a positive skin prick test and a positive RAST (class ≥ 2) to one of the tested standardized allergenic extracts: house-dust mite, cat dander, a mixture of five grass pollens, or birch pollen. Skin test positivity was defined as a wheal surface area larger than or equal to that of a positive control, and at least 10 mm^2 in size.

Asthmatic patients treated with corticosteroids and/or long-acting β_2-agonists were excluded. Other major exclusion criteria included a prolonged corrected QT interval on the ECG. The prior use of certain medications within defined time limits also constituted exclusions: these included astemizole, ketotifen, systemic long-acting corticosteroids, or immunoglobulins within 2 months; local corticosteroids at the site of the local skin test within 3 months; and nasal, bronchial, or other short-acting corticosteroids, antihistamine drugs, ketoconazole, itraconazole, or macrolide-type antibiotics within 2 weeks.

Treatment

Nonsymptomatic patients were assigned by a computer-generated randomization scheme to receive either ebastine 20 mg or placebo once daily for 7 days. Study medications were dispensed as blister packages of seven capsules containing either two tablets of ebastine 10 mg or placebo. Patients took their medication for 7 days in the morning.

Skin prick testing

All skin prick tests were performed by the same investigator, with a skin prick lancet (Stallergènes, Les Ulis, France). The skin prick test with the specific allergen extract was performed in each patient at 6 and 24 h after the last dose of medication, and at days 2, 3, 4, 5, 6, and 7. The tests were always accompanied by a positive (codeine phosphate 0.9%) and a negative (glycerol) control. Skin prick tests with increasing concentrations of histamine (0, 1, 5, 10, and 50 mg/ml) were conducted at enrollment, and at 6 and 24 h, and at day 5 after the last dose of medication. The measurements of the surface areas of the wheal and of the flare reactions were recorded 15 min after challenge. The borders of the skin reactions were marked on a translucent tape, scanned, and analyzed by computerized image programs, as previously described (13, 14, 16).

Adverse events

Subjects were questioned at each visit regarding possible adverse events. Safety parameters included the number and type of adverse events, ECG profiles, and laboratory data, all of which were determined before and after treatment.

Expression of results and statistical analysis

The efficacy analyses were carried out on the per-protocol population (23 patients). The safety analyses were carried out on the intention-to-treat (ITT) population of 27 patients. In all analyses, surface areas of wheal and flare reactions were expressed in mm^2 and were log (natural) transformed prior to analysis. The primary variable was defined as the wheal response to allergen assessed 5 days after the last dose of the test treatment. Flare response to allergen and response to histamine were considered secondary.

Table 1. Baseline patient characteristics (ITT population)

	Ebastine ($n=14$)	Placebo ($n=13$)
Sex		
M	8	6
F	6	7
Age, years		
Mean ± SD	23.4 ± 2.78	24.5 ± 2.8
Range	20.2–30.8	21.2–31.3
Weight, kg		
Mean ± SD	65.1 ± 12.4	60.9 ± 10.4
Range	49–93	46–83
Height, cm		
Mean ± SD	172.9 ± 10.2	170.8 ± 9.5
Range	158–186	155–184
No. of patients with allergic symptoms		
Rhinitis	14	13
Conjunctivitis	13	11
Asthma	7	4
Seasonal	3	6
Perennial	11	7

The allergen responses were analyzed by one-way analysis of covariance with the pretreatment surface area as covariate, for each time point after treatment. Confidence intervals (CI) of 90% were calculated for the contrast between treatments.

For the histamine dose-response curves, the two treatments were compared at each time-point after treatment with a linear model, with treatment and patient within treatment as factors, and log histamine concentration as covariate (zero histamine was not included in these comparisons). Heterogeneity of slope between treatments was investigated and a common slope fitted if appropriate. If the lines were nonparallel (i.e., heterogeneous slopes), the two treatments were compared at each concentration by one-way analysis of variance.

All treatment comparisons were based on a 5% one-sided significance level with the exception of the allergen challenge at 6 h (5% two-sided significance level).

The numbers of patients reporting adverse events per treatment were compared by two-tailed Fisher's exact test. Changes in laboratory and ECG data were evaluated by two-sample *t*-test (5% two-sided significance level).

Results

Wheal and flare responses to allergen

The wheal response to allergen after treatment with placebo progressively decreased over time from 6 h after treatment to day 4 (geometric means from 33.8 to 14.9 mm^2), and then slightly increased (geometric mean 22.2 mm^2 at day 7) (Fig. 1a). After ebastine, highly significant ($P < 0.01$) inhibition of the wheal surface area was observed at 6 h, 24 h, and day 2 after treatment as compared with placebo (ratios and 90% CI of 0.21 [014, 0.32], 0.24 [0.13, 0.44, and 0.33 [0.16, 0.66], respectively) (Fig. 1a). The inhibition of wheal response was less pronounced at day 3 (ratio and 90% CI 0.61 [0.37, 0.99]). From days 4 to 7 after

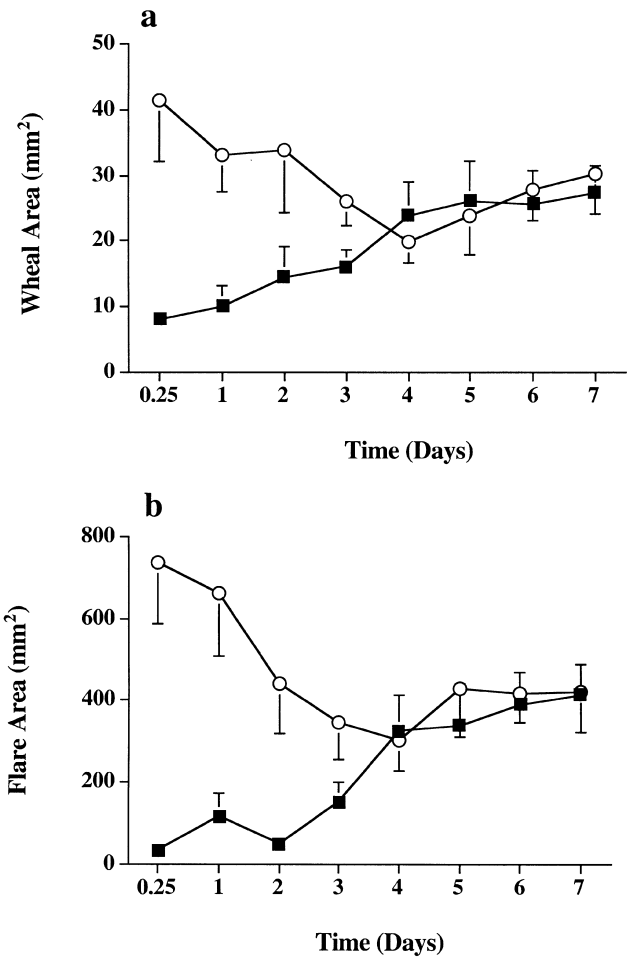

Figure 1. Wheal (a) and flare (b) surface area induced by antigen in function of time (days) after discontinuation of 7-day treatment with either ebastine (■) or placebo (○). No significant difference between ebastine and placebo groups was observed by days 4 (wheal) and 3 (flare) after treatment. Points are means, and bars are SEM of results obtained in 23 patients.

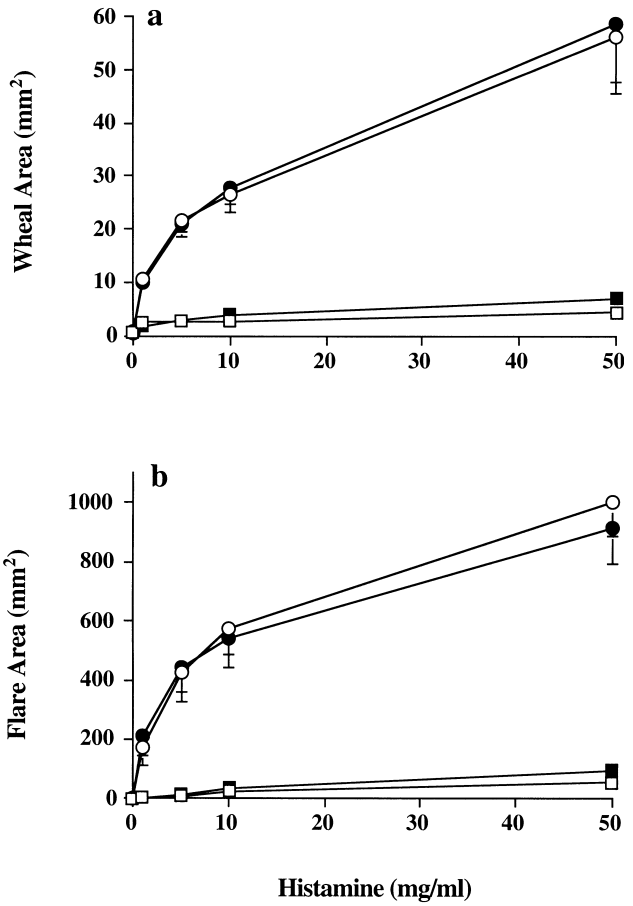

Figure 2. Wheal (a) and flare (b) surface area induced by histamine skin prick test 6 h (open symbols) and 24 h (closed symbols) after treatment. Curves on ebastine (□, ■) were significantly different from placebo (○, ●). Points are means, and bars are SEM of results obtained in 23 patients.

treatment discontinuation, no significant difference in the allergen-induced wheal surface area was observed between the ebastine and placebo groups (ratios and 90% CI of 1.25 [0.67, 2.32], 1.23 [0.64, 2.36], 0.89 [0.50, 1.58], and 1.04 [0.64, 1.70] for days 4, 5, 6, and 7, respectively). Compared to a predetermined lower limit for a clinical effect of 0.42, ebastine was considered to have no clinical effect from day 4 onward.

The flare response to allergen after treatment with placebo also decreased over time from 6 h after treatment to day 4 (from 677.3 to 91.0 mm^2), and then slightly increased (300.8 mm^2 at day 7) (Fig. 1b). After ebastine treatment, a marked inhibition of the flare response was observed between 6 h and day 2 after treatment as compared with placebo ($P<0.01$ for each) (Fig. 1b). The flare response then returned to the placebo values: no significant difference in the flare surface area was observed between the ebastine and the placebo groups from days 3 to 7 after discontinuation.

Wheal and flare responses to histamine

A marked inhibitory effect of ebastine was seen on the histamine-induced wheal surface area at 6 and 24 h after treatment completion as compared with placebo (maximum wheal surface area at histamine 50 mg/ml ranging from 0 to 23.9 mm^2 as compared with 19.9 to 184.8 mm^2). The slope of the response lines to histamine for ebastine and placebo was clearly non-parallel at 6 and 24 h (Fig. 2). In contrast, at day 5 after treatment, histamine produced similar concentration-response curves for the ebastine and the placebo groups (not shown). The lines were parallel, indicating no residual effect of ebastine compared to placebo 5 days after treatment discontinuation.

Marked inhibition of the histamine-induced flare surface area was seen after ebastine treatment at 6

and 24 h as compared with placebo (maximum flare surface area at 50 mg/ml histamine ranging from 7.5 to 323.3 mm^2 and 437.6 to 1867.0 mm^2, respectively). The response lines for ebastine and placebo were clearly nonparallel at 24 h (Fig. 2b). In contrast, at day 5 after treatment, histamine produced concentration-response curves that were not statistically different between ebastine and placebo (not shown). In addition, the lines were essentially parallel (although anomalous values were seen at 1 mg/ml), indicating no residual effect of ebastine compared to placebo 5 days after treatment discontinuation.

Adverse events

During the 7 days of treatment, 10 patients treated with ebastine reported a total of 24 adverse events. No serious adverse event occurred. The most commonly reported event was somnolence (six cases), followed by abdominal pain (two cases), diarrhea (two cases), dry mouth (two cases), and fatigue (two cases). During the 7-day period on placebo, eight patients reported a total of 11 adverse events, most commonly involving headache (two cases) and somnolence (two cases). No patient discontinued the study because of an adverse event. ECG data collected before and after treatment showed no abnormalities in cardiac rhythm or QT intervals in either study group. No biologic changes were reported.

Discussion

The results of this study clearly define the time period required for the inhibitory effects of ebastine on allergen-induced skin reactivity to disappear. Administration of ebastine at 20 mg per day in a double-blind, placebo-controlled fashion for 7 days ensured that a pharmacokinetic steady state was achieved. After drug discontinuation, the wheal and flare surface areas to allergen were markedly inhibited for the first 2 days in patients who had taken ebastine as compared with those who had received placebo, showing good efficacy of ebastine for 48 h after treatment. No difference in the wheal and flare surface areas was present by day 4, showing that positivity of the skin response to allergen returns 4 days after ebastine discontinuation. Results of the histamine challenge test performed at day 5 confirmed the allergen test outcome, i.e., that no residual inhibitory effect of ebastine could be detected.

The variables used in this study were the sizes of the wheal and flare surface areas in response to allergen and to exogenous histamine. These are widely accepted to demonstrate the pharmacodynamic activity of antihistamines (13, 14, 16–19). The sensitivity, specificity, and reproducibility of the skin prick test are good, especially for the wheal response to allergen (20, 21) and histamine (13, 14). In contrast, it is noticeable that the flare responses are highly variable in response to antigen, a finding which is probably related to the fact that the flare response is not entirely histamine-dependent. We have been willing to select patients from a large allergenic population, rather than from a population showing specificity to an allergen, leading to the use of a large panel of allergenic extracts in this study. The main reason for that derived from the objective of our study, which was dedicated to establish the time period during which ebastine treatment should be stopped in allergic patients before skin prick testing is performed for characterization of the sensitizing allergen. Hence, the conclusions related to this large allergic population of our study should be applicable to allergologic clinical practice.

The duration of the inhibition of the skin response produced by an antihistamine has direct relevance to the results and interpretation of skin prick tests, which are commonly used for the diagnosis of allergic disorders. To ensure the accuracy of such tests, antihistamines must be discontinued for an appropriate period of time before the test. Almind et al. (22) studied the post-treatment inhibitory effect of various antihistamines after a 2-day administration period. The duration of inhibition after the last dose, defined when wheal and flare reactions had returned to baseline $\pm$ SD, was noted to be 17-28 days with astemizole, and 4–7 days with loratadine and terfenadine. More recently, the International Consensus Report on the Diagnosis and Management of Rhinitis recommended that first-generation antihistamines be stopped for 2–4 days before a skin test, that astemizole should be stopped for 6–8 weeks, and that other second-generation antihistamines should be discontinued for 1 week. In contrast, the results of the current study indicate that ebastine should be discontinued for 4 days before a diagnostic skin test in order to interpret the results reliably and correctly, and diagnose allergy. This represents a significant clinical advantage for allergy patients who rely on antihistamine use for relief of severe or bothersome symptoms.

In conclusion, we have shown that the inhibition of skin reactivity to an allergen disappears completely 4 days after the last dose of treatment with ebastine 20 mg/day. Therefore, patients using ebastine who require a skin prick test need to be ebastine-free for this short period of time.

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