

Therapeutic effect of loratadine on pruritus in patients with atopic dermatitis

A multi-crossover-designed study

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The aim of the study was to assess the therapeutic efficacy of loratadine on pruritus in patients with atopic dermatitis, considering the patients' sensation of itch. Sixteen patients, mean age 24.8 years, with moderate or severe atopic dermatitis were included in a double-blind and placebo-controlled study with a six-period, multi-crossover design. The patients were given 10 mg loratadine or placebo every day, alternating between loratadine and placebo every 2 weeks. The degree of pruritus during the day and during the night was recorded by the patients every morning and every evening, respectively, on a 10-cm visual analog scale. The study detected a significant effect of loratadine, as compared with placebo, on pruritus during the day, pruritus during the night, and severity of rash. At least nine of the 16 patients included were classified as responders and only one as a nonresponder to loratadine treatment. It is concluded that loratadine may be tried as an adjuvant therapy in the management of severe and moderate atopic dermatitis, in patients complaining of pruritus.

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The pathogenesis of atopic dermatitis (AD) is unknown. Apparently, there is an interaction between the immune system and the skin, leading to an inflammation in which a number of mediators are involved. The disturbances in the immune system are characterized by a tendency to increased IgE synthesis, imbalance in the regulation of T cells, and increased release of mediators from leukocytes (17). Enhanced release of histamine from basophils of atopic subjects has been found in *in vitro* studies (5). Furthermore, elevated levels of histamine have also been found in involved skin in atopic dermatitis (16). Yet, the clinical significance of histamine in the inflammatory process of atopic dermatitis is debated.

On the basis of studies demonstrating no effect of nonsedating antihistamines on pruritus in atopic dermatitis, it has been claimed that histamine plays no significant role in the pathogenesis of atopic dermatitis (4, 12, 18). On the other hand, there are some reports indicating that there may be some effect of these drugs on pruritus in AD (3, 7).

Although histamine does not seem to be an important mediator of the inflammation of the skin in atopic dermatitis, it may be a contributing factor, together with other mediators. From a clinical point

of view, it has been pointed out that even a slight reduction of pruritus may be a significant improvement in quality of life for patients with severe atopic dermatitis (7).

The aim of this study was to assess the effect of loratadine on pruritus in patients with atopic dermatitis, considering the patients' sensation of itch. The study was designed to detect even a slight reduction of the pruritus, and, in addition, to distinguish between responders and nonresponders. This was important because from clinical experience we had the impression that the response was rather different in different patients, some reporting a good effect, whereas others experienced no benefits from this drug.

Material and methods

Patients

Seven female and nine male patients with pruritus caused by a moderate or severe degree of atopic dermatitis (9) were included in the study. The severity of the dermatitis was assessed on the basis of course of the disease, pruritus, and extent of dermatitis, as described elsewhere, by a score from 0 to 9

(15). The patients had an average age of 24.8 years (range: 19.5–37.3 years) and duration of disease of 24 years (range: 12–37 years). All patients experienced itching during the 10 days before entering the study. Pregnant or lactating women and patients receiving concomitant medication expected to interfere either with skin disorders or with the known mechanism of pruritus were excluded.

Fifteen of the patients had either allergic rhinitis, bronchial asthma, or both. Antihistamine treatment had previously been used by 10 of the patients. Written consent was obtained from all 16 patients.

Study design

A block-randomized, double-blind, single-center multi-crossover (MCO) trial (6, 11, 14) between 10 mg loratadine once daily and identical placebo tablets was used (Fig. 1). Before randomization, all the patients included were given topical steroid treatment (hydrocortisone 17 alpha-butyra) for 2 weeks, if needed. According to presence of pruritus at the end of this run-in period, the patients were divided into two blocks (Fig. 1). The MCO consisted of six periods, each of 2 weeks' duration. The patients from each of the two blocks were randomized in such a manner that one-half entered the MCO part with loratadine and one-half with placebo. The MCO model implies regular alternation between periods with the active drug and with placebo (6, 11, 14).

During the treatment periods, the patients were allowed to use emollients, and, if needed, a mild topical steroid ointment (hydrocortisone 17 alpha-butyra). However, a new treatment period was not started before the use of topical steroids had ended.

Study assessments

The history of atopic dermatitis and pruritus was initially recorded. Before inclusion, blood samples

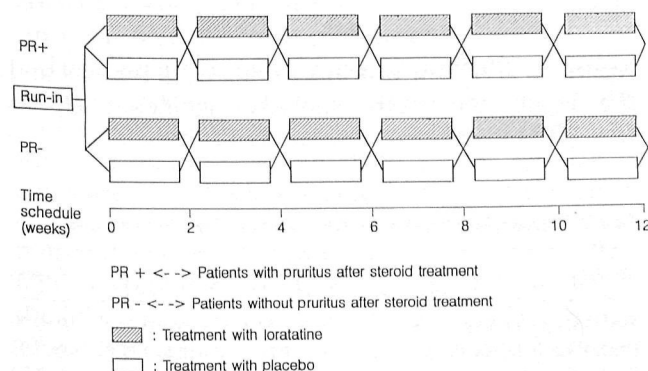


Fig. 1. Design of study. Patients were stratified into blocks according to occurrence of pruritus after steroid treatment before inclusion.

were taken from all the patients for total white blood cell count, circulating eosinophils count, and total IgE (Table 1). The patients were prick-tested for dog, cat, horse, birch, timothy, house-dust mite, mugwort, and *Cladosporium herbarum* (Phazet^R, Pharmacia, Sweden), Phazet histamine and Phazet negative being used as the positive and negative controls, respectively. The areas of the positive tests were used to express a score as follows: reactions like the positive reference (+ + +) = 1, half the size of the positive reference (+ +) = 0.5, and twice the positive reference or more (+ + + +) = 2. For each patient, the scores for each allergen were summarized as an index of the prick test ranging from 0 to 16 (Table 1). During the run-in period and each of the MCO periods, the patients recorded daily the degree of pruritus during the night and during the day on a 10-cm visual analog scale (VAS) (1, 14). The need for local steroids was evaluated by the investigator, and the average pruritus for the last 2 days and the severity of the rash were recorded by the patients on a 10-cm VAS at the end of each period. The study was conducted in the period October to April.

Definition and classification

The MCO X-score (X_s) was defined as the number of times loratadine had better effect than placebo in the preceding or following period (11). For each of the observed variables, an X-score was calculated for each patient at the end of the study. On the basis of previous trials (6, 11, 14), patients with $X_s \leq 1$ were classified as nonresponders to loratadine, patients with $X_s = 2$ were considered to be unclassifiable, and patients with $X_s \geq 3$ were classified as responders.

The differences in symptoms recorded on a 10-cm VAS in the loratadine period and both the preceding and following placebo periods were calculated for each patient on each variable. The efficacy index (EI) was defined as the mean of these five differences and was individually calculated (14). A positive EI

Table 1. Initial laboratory examinations and severity of disease

Variables	Mean values	95% Confidence intervals
White blood cell count ($10^9/l$)	6.6	(5.9–7.3)
Eosinophil ($10^6/l$)	523	(354–692)
Total IgE (u/ml)*	754	(558–950)
Prick-test index (score)**	6.6	(3.8–9.4)
Degree of atopic dermatitis (score)***	7.6	(6.9–8.4)

* Values ≥ 1000 u (nine patients) are truncated to 1000 in calculations.

** Sum of scores from prick tests with eight different allergens. Range of index is 0–16.

*** Maximum score: 9.

indicated a positive effect of loratadine, and a negative EI indicated the opposite.

Statistical methods

For estimation of the location parameters, the mean values with 95% confidence intervals were used. Student's procedure (10) was used to calculate the intervals. The area under the curve (AUC) was calculated by the Trapeze method (8). All tests comparing the effect of loratadine with placebo were one-tailed. Differences were considered to be significant if the *P* values were less than or equal to 5%. The Hotellings T^2 -method with specified hypotheses ($= 0$) was used to compare the effects of loratadine with placebo.

Results

Pruritus during the day and during the night was recorded daily in all the six trial periods. The mean degree of pruritus during the day in the first active treatment period was 2.4 cm on the VAS. This increased to 2.8 cm in the first placebo period and decreased again to 2.1 cm in the second active treatment period. From the second active period to the second placebo period, the mean degree of pruritus during the day increased to 2.6 cm, then decreased to 2.4 cm in the third active treatment period, and increased again to 2.5 cm in the third placebo period (Fig. 2a). The mean degree of pruritus during the night followed the same pattern as during the day. From the first active treatment period to the first placebo period, the mean degree increased from 2.4 to 2.7 cm. This mean degree was reduced to 2.1 cm in the second active treatment period and again increased to 2.6 cm in the second placebo period. From the second placebo period to the third periods, the mean degree of pruritus during the night was found to be nearly constant (Fig. 2b). The mean degree of pruritus recorded at the end of each treatment period followed the same pattern as pruritus during the day, with the highest degree in the placebo periods (Fig. 2c).

The mean number of days with use of local steroids during the six treatment periods and the mean severity of rash at the end of each treatment period followed the same pattern as pruritus during the night and during the day, respectively.

The study detected a statistically significant effect of loratadine, as compared with placebo (Table 2), for pruritus during the day ($P = 0.03$), pruritus at the end of each treatment period ($P = 0.03$), and severity of rash ($P = 0.05$). Additionally, the analysis indicates an effect of loratadine on pruritus during the night. However, the efficacy index was not significant ($P = 0.06$). By comparing the two groups with

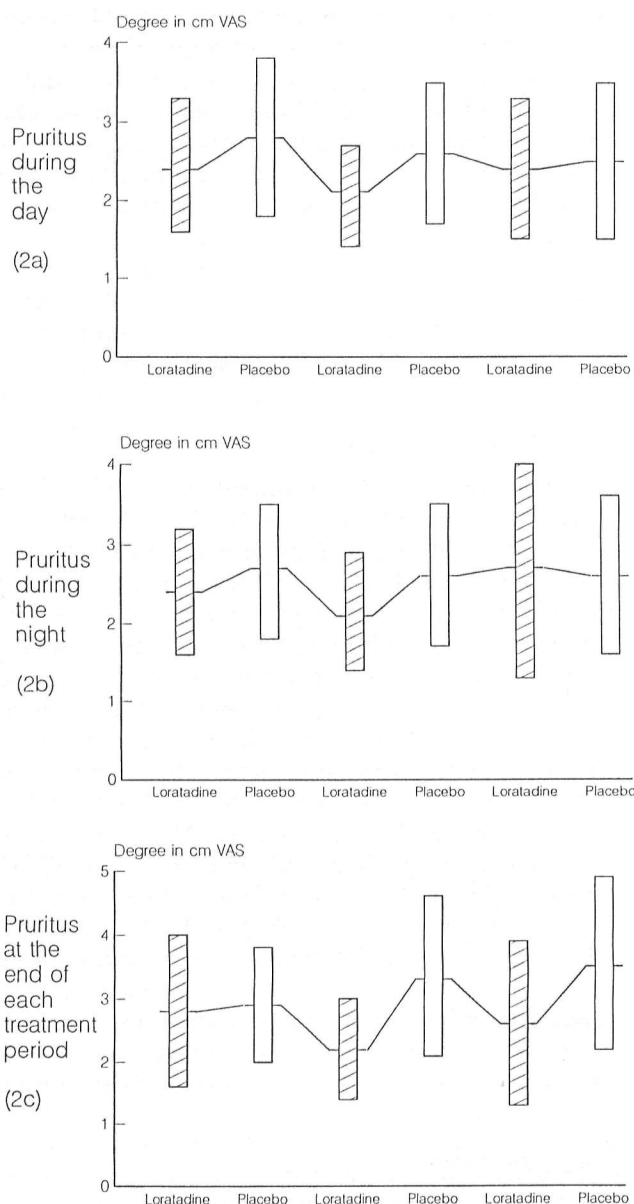


Fig. 2. Changes in pruritus recorded on visual analog scale (VAS) (maximum score: 10 cm) during day (2a), during night (2b), and at end of each treatment period (2c), expressed as mean values with 95% confidence intervals at each of six MCO periods.

regard to AUC for pruritus during both the day and the night, the study showed significant effects ($P = 0.03$) in favor of loratadine (Table 3).

Table 2. Efficacy indexes based on the five main efficacy variables in the study

Variables	Mean	95% Conf. int.	<i>P</i> values
Pruritus during the night	1.4	(-0.7-3.6)	$P = 0.06$
Pruritus during the day	1.7	(-0.4-3.8)	$P = 0.03$
Pruritus the two last days of each period	0.8	(-0.1-1.8)	$P = 0.03$
Number of days using local steroids	0.8	(-1.9-3.5)	$P = 0.12$
Severity of rash	1.2	(-0.3-2.8)	$P = 0.05$

Table 3. Area under the curve during the three treatment periods with loratadine and placebo. The results are expressed as mean values with 95% confidence intervals

Variable	Loratadine	Placebo	P values
Pruritus during the night	32.0 (21.1–42.9)	37.1 (25.9–48.3)	P=0.03
Pruritus during the day	31.9 (21.3–42.4)	37.0 (24.8–49.1)	P=0.03

By the MCO X-score procedure for classification of patients, 14 were classified as responders to loratadine, one was "unclassifiable" and one was classified as a nonresponder to loratadine on the basis of the variable "pruritus during the day". On the basis of "pruritus during the night", 11 patients were classified as responders, four were "unclassifiable", and one was classified as a nonresponder to loratadine. On the basis of the number of days with local steroids, three patients were classified as responders, nine were "unclassifiable", and four were classified as nonresponders to loratadine.

The sum of X-scores from these three variables was calculated for each patient. Nine of the patients had an X-score sum equal to or larger than 9 and were classified as responders; six had X-scores of 6, 7, or 8 and were "unclassifiable"; and one had a total X-score less than 6 and was classified as a nonresponder to loratadine.

All the included patients concluded the study, and no patients reported any side-effects during the trial.

Discussion

Loratadine was shown to reduce the sensation of itch better than placebo in this group of patients with moderate and severe atopic dermatitis. The difference was clearly detectable. The study design enabled us to distinguish between responders, unclassifiables, and nonresponders. Because of the limited number of patients included, we were unable to point out any characteristics typical of responders but not nonresponders. The test-power in these comparisons was too low to be performed.

The patients' assessment of the severity of rash at the end of each treatment period showed an improvement after the loratadine periods, as compared with the placebo periods. One should hesitate to conclude from this study that loratadine has a direct effect on skin lesions, as this judgment may simply reflect the reduced sensation of itch, or the effect may be secondary to a lesser degree of scratching in the loratadine periods than in the placebo periods. Objective methods for evaluation of the degree of dermatitis during the study were not used.

Although the study has shown a significant difference between placebo and loratadine with respect

to efficacy on pruritus in this group of patients with atopic dermatitis, the question arises whether this difference is clinically significant. In the "responder group", there was a 19% average reduction in VAS score for pruritus with loratadine over placebo. Considering this in combination with the safety profile for loratadine, we conclude that it is reasonable to try loratadine as an adjuvant therapy in the management of severe and moderate atopic dermatitis, in patients complaining of pruritus during daytime.

One should be cautious in concluding on the basis of such studies that histamine contributes to the inflammation of atopic dermatitis, as it is also possible that loratadine has other effects that interfere with the inflammatory process in atopic dermatitis. Studies of allergic rhinitis have reported that loratadine may help to stabilize mast cells and thus reduce the formation of leukotriene B₄ (LTB₄) (2). Therefore, the observed beneficial effect on pruritus in this study is not necessarily caused simply by an inhibitory effect on the H₁-receptors in the skin.

As previously described, the number of patients in this study was low ($n = 16$), but, because of the special study design, the testpower was sufficient (6, 11, 14). A problem may be that the population is not representative of a general population of patients with atopic dermatitis. In view of this, one should be cautious in extending the conclusions of this study to patients with a mild degree of atopic dermatitis, as such patients were not included in the study.

An antipruritic effect of nonsedative antihistamines has been reported for terfenadine and acrivastine as well, as found in a double-blind, placebo-controlled study (3, 7). There are also studies indicating that some nonsedating antihistamines are as effective as sedative antihistamines in studies comparing a nonsedative with a sedative antihistamine in patients with atopic dermatitis (3). However, it is difficult to establish conclusions from such studies if a placebo group is not included, because it can hardly be excluded that the reduction of pruritus observed in these studies is due to factors other than the antihistamines.

On the basis of the present study, we conclude that loratadine is better than placebo for pruritus in patients with moderate and severe atopic dermatitis, and that it is a useful adjuvant in the management of moderate and severe degrees of atopic dermatitis.

References

1. AABAKKEN L, LARSEN S, OSNES M. Visual analogue scales for endoscopic evaluation of nonsteroidal anti-inflammatory drug-induced mucosal damage in the stomach and duodenum. *Scand J Gastroenterol* 1990; 25: 443–8.
2. ANDERSSON M, NOLTE H, BAUMGARTEN C, PIPKORN U. Suppressive effect of loratadine on allergen-induced histamine release in the nose. *Allergy* 1991; 46: 540–6.

3. BEHRENDT H, RING J. Histamine and antihistamine and atopic eczema. *Clin Exp Allergy* 1990; 20 (Suppl. 4): 25–30.
4. BERTH-JONES J, GRAHAM BROWN RAC. Failure of terfenadine in relieving the pruritus of atopic dermatitis. *Br J Dermatol* 1989; 121: 635–7.
5. BUTLER JM, CHAN SC, STEVENS SR, HANIFIN JM. Increased leukocyte histamine release with elevated cyclic AMP-phosphodiesterase activity in atopic dermatitis. *J Allergy Clin Immunol* 1983; 71: 490–7.
6. DICKSTEIN K, KNUTSEN H. A double-blind multiple crossover trial evaluating a transdermal nitroglycerine system versus placebo. *Eur Heart J* 1985; 6: 50–6.
7. DOHERTY V, SYLVESTER DGH, KENNEDY CTC, HARVEY SG, CALTHROP JG, GIBSON JR. Treatment of itching in atopic eczema with antihistamines with a low sedative profile. *BMJ* 1989; 298: 96.
8. GIBALDI M. *Biopharmaceutics and clinical pharmacokinetics*. Washington, DC: Lea & Febiger, 1983.
9. HANIFIN JM, RAJKA G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol (Stockh)* 1980; 92: 44–7.
10. KENDALL M, STUART A. *The advanced theory of statistics*. Vol. II. London: Charles Griffin, 1979.
11. KLEVELAND PM, LARSEN S, SANDVIK L, et al. The effect of cimetidine in non-ulcer dyspepsia. Experience with a multicrossover model. *Scand J Gastroenterol* 1985; 20: 19–24.
12. KRAUSE L, SHUSTER S. Mode of action of H₁-antihistamines in itch. *Br J Dermatol* 1983; 24 (Suppl.): 109.
13. LARSEN S, AABAKKEN L, LILLEVOLD PE, OSNES M. Assessing soft data in clinical trials. *Pharm Med* 1991; 5: 29–36.
14. LARSEN S, FARUP P, FLATEN O, OSNES M. The multicrossover model for classifying patients as responders to a given treatment. *Scand J Gastroenterol* 1991; 26: 763–70.
15. RAJKA G, LANGELAND T. Grading of the severity of atopic dermatitis. *Acta Derm Venereol (Stockh)* 1989; Suppl. 144: 13–14.
16. RING J, SENTER T, CORNELL RC, ARROYAVE CA, TAN EM. Plasma complement and histamine changes in atopic dermatitis. *Br J Dermatol* 1979; 100: 521–30.
17. RUZICKA T, RING J. Enhanced releasability of prostaglandin E₂ and leukotrienes B₄ and C₄ from leukocytes of patients with atopic dermatitis. *Acta Derm Venereol (Stockh)* 1987; 67: 469–75.
18. SAVIN JA, DOW R, HARLOW BJ, MASSEY H, YEE KF. The effect of a new non-sedative H₁-receptor antagonist (LN 2974) on the itching and scratching of patients with atopic eczema. *Clin Exp Dermatol* 1986; 11: 600–2.

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