

Efficacy and safety of loratadine suspension in the treatment of children with allergic rhinitis

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The safety and efficacy of loratadine was compared with that of dexchlorpheniramine in children with allergic rhinitis. Twenty-one children received loratadine 0.11-0.24 mg/kg ideal body weight once daily and 19 dexchlorpheniramine 0.10-0.23 mg/kg every 8 h (0.30-0.69 mg/24 h) for 14 consecutive days. Both loratadine and dexchlorpheniramine were effective in reducing nasal and ocular symptoms in allergic children. Substantial improvement in allergy symptoms was observed at the first evaluation (day 3 of treatment) and was maintained for the study duration. No significant trend of abnormality in laboratory parameters was observed. Drowsiness was present only in the dexchlorpheniramine-treated group. Loratadine appears to be a simple, effective and safe therapy for seasonal allergic rhinitis.

Key words: allergic rhinitis; children; dexchlorpheniramine; loratadine; non-sedating antihistamine.

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Loratadine (SCH 29851) is a new antihistamine of the non-sedating class, with a selective binding to H_1 peripheral receptors and a structural formula similar to that of azatadine (17). Pre-clinical and clinical studies in adults have shown that loratadine has low toxicity and no significant central and autonomic nervous system activities, such as sedation and anticholinergic side effects (1, 6, 12, 15).

In animal studies it was demonstrated that its antihistaminic effectiveness is superior to that of the most known antihistamine drugs, such as diphenhydramine, mequitazine, astemizole, terfenadine and chlorpheniramine, but slightly inferior to that of azatadine (1). Its duration of action in animals suggested a once daily clinical use, which was later supported by pharmacokinetic studies in humans (8).

In the present study we compared the efficacy and safety of loratadine administered once a day with that of dexchlorpheniramine adminis-

tered three times a day in the management of seasonal allergic rhinitis in childhood.

PATIENTS AND METHODS

Forty children, aged 4-12 years (mean 7.7) 26 males and 14 females, with moderate to severe seasonal allergic rhinitis were selected for the study conducted during the spring allergy season (April to June) of 1986. Prior to the initiation of treatment, written informed consent was obtained from the parents. To enter the study each child's hypersensitivity had to be confirmed by allergy history and a positive response to skin prick test (allergen wheal diameter 3 mm > histamine control (11)) to seasonal allergen (grass pollen, parietaria). The children or their parents should also be capable of recording the daily symptom score on a diary card, complying with the dose regimen and able to maintain the study evaluation schedule.

Children with a history of asthma or on immunotherapy with pollen extracts, or requiring treatment which could interfere with the results, were excluded from the study. Also excluded were patients with nasal polyps, abnormal laboratory test parameters, multiple drug allergies, or a history of idiosyncratic reaction to antihistamines. Patients should not have used antihistamines or decongestants within 24 h prior to initiation of treatment, cromolyn sodium, terfenadine or astemizole within the previous 2 weeks, or corticosteroid preparations within the previous month.

At baseline, patients had to be symptomatic, and allergy symptoms were assessed and rated numerically according to severity to establish baseline symptom score. Laboratory test values, ECG, rhinoscopy and vital signs were also evaluated. The children were then randomly assigned to receive loratadine 5 ml (5 mg) (1 mg/ml suspension) once daily in the morning, always at the same time, or dexchlorpheniramine 2.5 ml (1 mg) (1 mg/2.5 ml syrup) every 8 h for 14 consecutive days. Children under 6 years and those weighing less than 20 kg received half dose. Treatment bottles were returned weekly at visit and the contents verified for compliance. Clinical evaluation was based on the investigator's and patient's (or his parents') assessment of nasal and non-nasal symptoms.

The symptoms evaluated at baseline and at the three clinic visits (days 3, 7 and 14) by the investigator were: nasal discharge, nasal stuffiness, nasal itching and sneezing, itching burning or watery eyes, redness of eyes, itching ears or palate. The same symptoms were evaluated at baseline and daily throughout the study period by the patient or his parents.

The severity of each symptom and the overall condition of rhinitis were rated and scored numerically on a scale of 0 (none) to 3 (severe). To initiate treatment, two of the four nasal symptoms had to be at least moderate (score = 2) and the total score of nasal symptoms plus itching of eyes at least 6. The patients' symptoms were evaluated throughout the study by the same investigator (P. M.) who was unaware of the treatment regimen (loratadine or dexchlorpheniramine). The parents had been carefully instructed

in the importance of keeping the investigator (P. M.) "blind" to the drug being used and to avoid any discussion about the treatment regimen. The overall therapeutic response was scored from 4 to 0, 4 being excellent: virtually all symptoms eliminated, and 0: treatment failure.

Blood pressure, body temperature, pulse and respiration rate were recorded at each visit, while clinical laboratory tests, ECG, body weight and height were evaluated at baseline and at the end of the study. At each visit, in order to detect any adverse effects, the children and their parents were asked whether they had noticed anything unusual since the previous visit. Date, time of onset, duration and severity of any adverse experience were recorded and the relation of side effects to study treatment assessed.

Pollen collection was performed with a Burkard (Hirst) spore trap. In this pollen sampler air is drawn into the device at 10 l/min, and a continuous particle deposit with time discrimination is developed on a tape-coated drum providing a 7-day record. Pollen counts were performed throughout the study period.

Statistical analysis

The homogeneity before treatment between the two groups of patients has been assessed by chi-square test for qualitative variables (measured by nominal or ordinal scales) or one-way Anova for quantitative variables (measured by interval or ratio scale) (15). An evaluation of the efficacy of the two drugs was made taking into account the sum of the symptom scores by linked factorial analysis of variance for repeated measures, with factor "drug" fixed at two levels, factor "time" fixed at different levels (depending on the frequency of patient examination) and factor "patient" randomly nested into the fixed factor drug.

The differing efficacy resulting from unequal demand is allowed for by the statistical significance of the interaction "time $\times$ drug" which tests the null hypothesis of no difference between the drugs examined in this analysis. In this case a two-way Anova with repeated measures for each treatment group was performed independently. Mixed factorial Anova and two-way Anova (if

the interaction time $\times$ drug proved statistically significant) test the null hypothesis of no difference between the times when both drugs were used (mixed factorial Anova, and for each drug separately, two-way Anova). In addition, sum of squares due to factor "time" has been divided into a linear quadratic, cubic trend by the orthogonal polynomial method. Because measurements were repeated on the same subjects, the significance of the factor "between patients", i.e. time and interaction "time by drug", have been corrected according to the Greenhouse-Geisser approach (7). Qualitative variables rating the global efficacy of the treatment have been evaluated by the chi-square test.

RESULTS

Among the 40 children selected, 21 received loratadine and 19 dexchlorpheniramine. Doses were in the range 0.11–0.24 mg/kg (2.5–5 mg/daily) for loratadine and 0.10–0.23 mg/kg (1.5–3 mg) for dexchlorpheniramine.

No significant statistical differences were observed between the treatment groups for all parameters considered at the initial examination (Table 1). Even though loratadine-treated patients were always exposed to higher pollen counts, differences between the two groups were not statistically significant ($P = 0.09$).

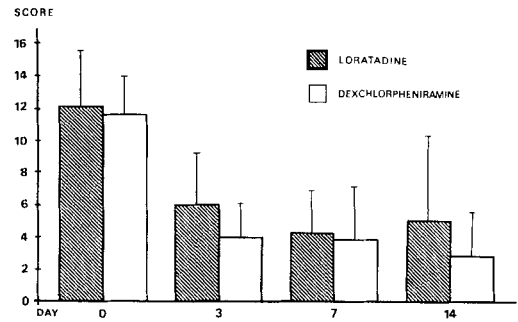


Fig. 1. Evolution of symptoms (nasal discharge, stuffiness, itching and sneezing, itching or burning eyes, watery eyes, redness of eyes, itching of ear or palate) expressed as mean total score, evaluated by the investigator during the treatment period with loratadine and dexchlorpheniramine (means and SD).

Severity of symptoms, expressed semiquantitatively by means of each patient's total symptom score, showed improvement with both drugs ($P < 0.01$) during the 14-day treatment period, both on physical examination (Fig. 1) and subjective symptoms (Fig. 2), confirming the equivalence of the assessments made independently by the investigator and the patient or his parent. Although the response tended to be better with dexchlorpheniramine than loratadine, no statistical difference between the treatment groups was evident ($P = 0.295$).

Table 1

Basal conditions (mean $\pm$ SD)

	Loratadine	Dexchlorpheniramine	
No. patients (M/F)	21 (14/7)	19 (12/7)	
Age (years)	7.6 $\pm$ 2.9	7.8 $\pm$ 3.0	NS
Body weight (kg)	25.2 $\pm$ 6.8	28.6 $\pm$ 10.3	NS
Height (cm)	122.1 $\pm$ 16.7	125.6 $\pm$ 17.4	NS
Body temperature ($^{\circ}$ C)	36.4 $\pm$ 0.3	36.3 $\pm$ 0.3	NS
Pulse rate (beats/min)	76.1 $\pm$ 7.1	75.1 $\pm$ 10.7	NS
Respiration rate (n./min)	22.9 $\pm$ 3.5	24.9 $\pm$ 3.9	NS
Systolic pressure (mmHg)	104.0 $\pm$ 7.4	104.0 $\pm$ 9.0	NS
Diastolic pressure (mmHg)	67.0 $\pm$ 9.0	66.0 $\pm$ 5.0	NS
Duration of allergy (years)	3.2 $\pm$ 1.3	2.5 $\pm$ 1.8	NS
Duration of last episode (days)	17.9 $\pm$ 8.2	20.1 $\pm$ 10.1	NS
Diameter of control wheal (mm)	4.5 $\pm$ 0.9	4.1 $\pm$ 1.3	NS
Diameter of allergen wheal (mm)	10.0 $\pm$ 2.6	9.1 $\pm$ 2.7	NS

NS = not significant

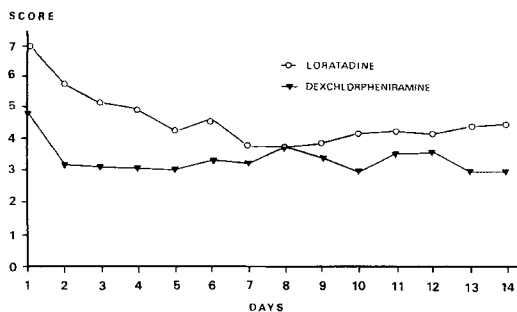


Fig. 2. Evolution of symptoms (nasal discharge, stuffiness, itching and sneezing, itching or burning eyes, watery eyes, redness of eyes, itching of ear or palate) expressed as mean total scores, recorded daily by the patients or their parents.

Rhinoscopy showed no statistically significant difference between the two treatments and both were associated with a significant reduction in nasal secretion and nasal stuffiness.

The evaluation of therapeutic results by both the investigator and the patient/parent had superimposable positive results with both drugs ($P > 0.05$) at each visit.

Since patients weighing less than 20 kg received half doses, the most important parameters (total symptoms score, nasal and ocular symptom scores, therapeutic response, side-effect incidence) were statistically processed for significant differences between subsamples. The results in the four subsamples (two treatment groups each divided into two dose groups) showed complete superimposition: i.e., both drugs develop effective therapeutic activity ($P < 0.01$) with equivalent trend ($P > 0.05$) independently of the dosages administered. These subsamples results are coincident with those recorded in the total sample.

Four of the 40 children stopped treatment before the end of the study: one dexchlorpheniramine-treated child because of failure on the 4th day, of three loratadine-treated two because of treatment failure after 7 and 12 days, respectively, and one because of nausea, vomiting and lipothymia on the 7th day. These symptoms were probably unrelated to the treatment since loratadine was given openly to the patients after 1 week and no side effects were observed.

Four children receiving dexchlorpheniramine showed somnolence on day 1, two other patients

complained of mild epistaxis during the first 3 days of treatment. Two children in the loratadine group had two episodes of moderate epistaxis, one on days 1-2 and the other on days 6-8, no child reported drowsiness. Haematological counts and biochemical analysis (electrolyte balance, liver and kidney function) showed that loratadine and dexchlorpheniramine at the dosages used were devoid of toxic effects.

DISCUSSION

The sedation caused by classical antihistamines has been a major drawback in the treatment of allergic rhinitis. New non-sedating antihistamines are now available. Among these, loratadine has been evaluated in adult patients for its safety and efficacy in seasonal allergic rhinitis using a 40 mg dose once a day (2, 3) and 10 mg dose once a day (4). All three studies reported the incidence of drowsiness with loratadine to be the same as that seen with placebo, and the drug was significantly superior to placebo and no different from mequitazine, terfenadine or clemastine in suppressing symptoms.

In the present study the ability of loratadine to ameliorate hay fever symptoms in children was similar to that of dexchlorpheniramine. Dexchlorpheniramine, however, induced a higher degree of sedation than loratadine: 100% of the loratadine-treated children were sedation free for the whole duration of the trial versus 79% of the dexchlorpheniramine-treated.

Our children received randomized treatment without the use of a double dummy technique because the dose, onset and duration of efficacy, as well as tolerance and adverse reactions to loratadine were unknown factors in the treatment of allergic children. This may be acceptable in children when a drug is new (10). We were careful to reduce all possibility of the investigator knowing the treatment regimen. The parents were instructed not to reveal the prescribed treatment to the children's examiner (P. M.) and no question was asked by the examiner in charge for an objective assessment. Side effects were reported on diary cards which were evaluated by different doctors. A placebo group, which would have increased the power of our observation, was not

included for ethical reasons since the study was performed in children who also had severe rhinitis.

Classical antihistamine therapy is problematic even in school-age children because of such side effects as sedation, subtle changes in school performance (9) and the frequent dosing intervals required for many of the older liquid preparations. A once-a-day regimen is possible with loratadine since it is rapidly distributed via the blood into extravascular space and is eliminated with a half-life of 18.7 h (13). Furthermore, a study of histamine-induced skin wheals after multiple doses of loratadine in adults (14) has shown that this effect is dose-related, occurs within 2 h of the first dose and is effective throughout the 28 days' treatment. Pharmacokinetically, (5, 13) together with rapid onset of action and lack of sedative effects and good tolerance (4, 14), loratadine appears to be a useful advance in the treatment of children with allergic rhinitis. Factors that seemed to have affected the response were the severity and nature of symptoms: the treatment failures in both the dexchlorpheniramine group and the loratadine group were highly atopic and complained mainly of no change in the degree of nasal obstruction during treatment.

This preliminary experience with loratadine at a once daily dosage of 0.11–0.24 mg/kg ideal body weight suggests that the drug is safe and effective for the treatment of allergic rhinitis in children. Further studies with a larger number of patients and the use of a placebo group will be needed to confirm our observations.

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