

Comparison of the effects of loratadine and astemizole in the treatment of children with seasonal allergic rhinoconjunctivitis

Boner AL, Richelli C, Castellani C, Marchesi E, Andreoli A. Comparison of the effects of loratadine and astemizole in the treatment of children with seasonal allergic rhinoconjunctivitis. *Allergy* 1992; 47: 98–102.

A. L. Boner, C. Richelli, C. Castellani, E. Marchesi, A. Andreoli

Pediatric Clinic, University of Verona, Italy

The efficacy and safety of a once-daily dose of loratadine 10 mg (5 mg in patients whose body weight was ≤ 30 kg) and astemizole 2 mg/10 kg body weight o.d. were compared in a 14-day third-party blind study.

Forty-one children (30 boys and 11 girls, aged 6–14 years) with seasonal allergic rhinoconjunctivitis entered the study. The pollen count was monitored throughout the study. A significant improvement ($p < 0.01$) in allergy symptoms was observed from the third day for both drugs; there was no significant difference between drugs, although loratadine led to a greater reduction in symptoms. In the astemizole group, the apparently rapid onset of drug action might be explained by reduced pollen exposure.

Therapeutic response was excellent/good in 83.3% and 58.8% of the loratadine and astemizole groups, respectively. The results reported by the patients/parents were similar. Nine of the children on astemizole and four children on loratadine complained of side effects; three patients in the astemizole group were withdrawn from treatment because of adverse effects. No abnormal changes in lab values were observed in either group.

Key words: astemizole; children; loratadine; seasonal allergic rhinoconjunctivitis

A.L. Boner
Clinica Pediatrica
Università di Verona
Policlinico Borgo Roma
37134 Verona
Italy

Accepted for publication 25 May 1991

Histamine H_1 -receptor antagonists are widely used in the management of allergic disease, especially hay fever (1–9). For many subjects, however, the use of these drugs is restricted by adverse effects such as sedation and dry mouth after conventional therapeutic doses. In recent years, newer non-sedating antihistamines have been developed that do not readily enter the central nervous system or interact with the neuroreceptors associated with sedation and therefore produce fewer undesirable side effects (4).

Astemizole, a new long-acting, highly selective histamine H_1 antagonist, has been shown to be significantly more effective than placebo and more potent than all reference antihistamine compounds (10) in the treatment of seasonal allergic rhinitis.

To date, astemizole and loratadine (6–8), another long-acting non-sedating selective peripheral histamine H_1 receptor antagonist, have not been compared in children. In this study we compared the efficacy of astemizole with that of loratadine, assessed in terms of their ability to relieve symptoms in children with seasonal allergic rhinitis.

Patients and methods

Patients

This study was performed in 41 children 30 boys and 11 girls, ranging in age from 6 to 14 years. All of the patients were suffering from moderate or severe seasonal allergic rhinoconjunctivitis and had positive skin prick tests (antigen-induced wheal diameter at least 3 mm $>$ that induced by the diluent control measured 15 min after exposure) to common spring allergens such as grass pollen and/or *Parietaria officinalis*.

Patients with asthma, idiosyncratic reactions to antihistamines or other drugs, or with any evidence of severe disease or abnormalities were excluded from the study. Patients were also excluded if they had used topical or systemic corticosteroids within 1 month or antihistamines and cromolyn within 7 days of the start of the study, or if they had been treated with specific immunotherapy. The children had never used astemizole or loratadine before the trial. Informed consent was obtained and the protocol was approved by the Hospital Ethics Committee.

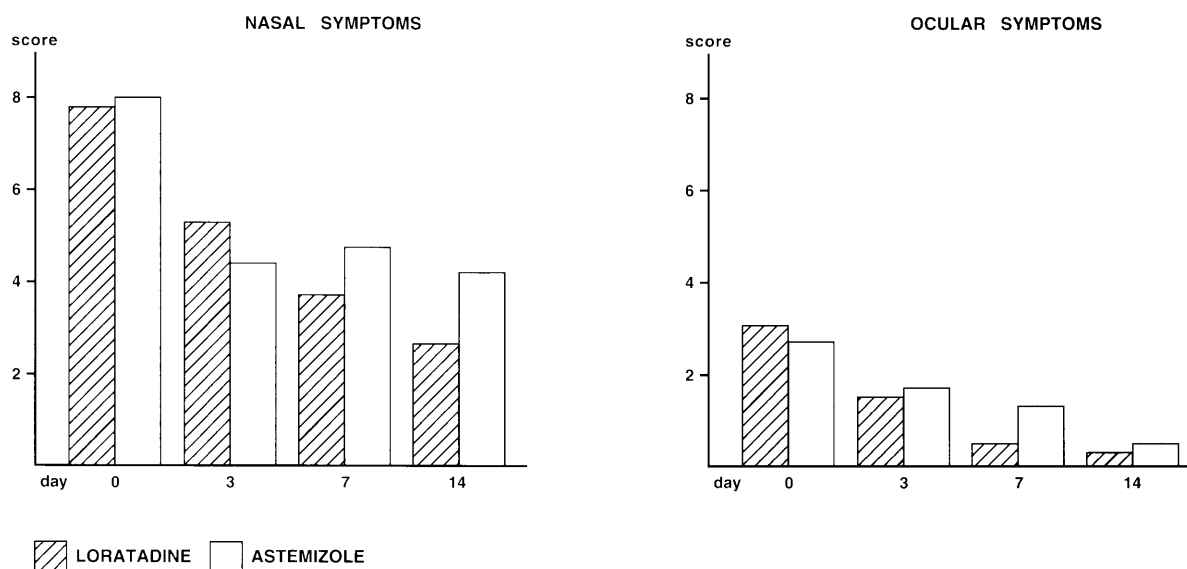


Fig. 1. Severity of nasal and ocular symptoms as assessed by the investigator during the study period.

Study design

This was a 14-day single blind, randomized, parallel-group study comparing the efficacy and safety of once daily doses of loratadine and astemizole in the treatment of seasonal allergic rhinoconjunctivitis. The study was performed between May and June 1988. Patients were evaluated at five separate study visits: on screening, on entry, and after 3, 7 and 14 days of treatment. During the screening visit, a clinical history was taken and a physical examination, rhinoscopy and skin prick tests were performed. Blood samples for haematological counts and biochemical analysis were taken both before treatment and at the end of the trial. Following the screening visit, the children were randomly assigned to receive loratadine or astemizole suspension once daily in the morning for 14 days.

In the loratadine group, 12 children with a body-weight of ≤ 30 kg received the dose of 5 ml (5 mg) and nine children with a body-weight > 30 kg received 10 ml (10 mg). In the astemizole group, children received the dose of 1 ml (2 mg)/10 kg body-weight.

At entry, patients had to be symptomatic and allergy symptoms (nasal discharge, nasal stuffiness, nasal itching and sneezing, itching, burning or watery eyes, eye-redness, and itching ears or palate) were assessed and rated numerically according to severity in order to establish a baseline symptom score. A four-point scale was used, with: 0 = no symptoms to 3 = severe. To initiate treatment, at least two of the nasal symptoms had to be moderate (score = 2) and the total score of nasal symptoms plus itching eyes had to be ≥ 6 .

During the subsequent study visits, the same

symptoms were evaluated always by the same investigators (C.R., C.C.) who were unaware of the treatment regimen. Patients were carefully instructed as to the importance of keeping the investigators "blind" to the drug being used and to avoid discussing the treatment regimen. Patients or their parents were asked for their daily evaluation of symptoms and side effects using the same rating system.

Treatment bottles were returned weekly and the contents verified to check for compliance by a different investigator (A.L.B.).

The children or their parents had to be capable of recording their daily symptom score on a diary card, complying with the dose regimen and able to maintain the study visit schedule. The results were recorded as excellent (total absence of symptoms), good (marked improvement and few symptoms), moderate (slight reduction in symptoms) or poor (no improvement or symptoms worse than baseline). At the second and the final visit, body-weight was recorded. The safety of the two treatments was evaluated on the basis of the occurrence of adverse reactions and laboratory test results. The investigators judged the relationship of an adverse experience to treatment as probable, possible or unrelated, as well as its degree of severity (mild, moderate or severe). Pollen count was monitored throughout the study period.

Statistical analysis

The homogeneity between the two groups and the comparison of scores at different times of observation was assessed by using the chi-square (or Fisher's exact test). Treatment effectiveness was analysed according to mixed factorial ANOVA.

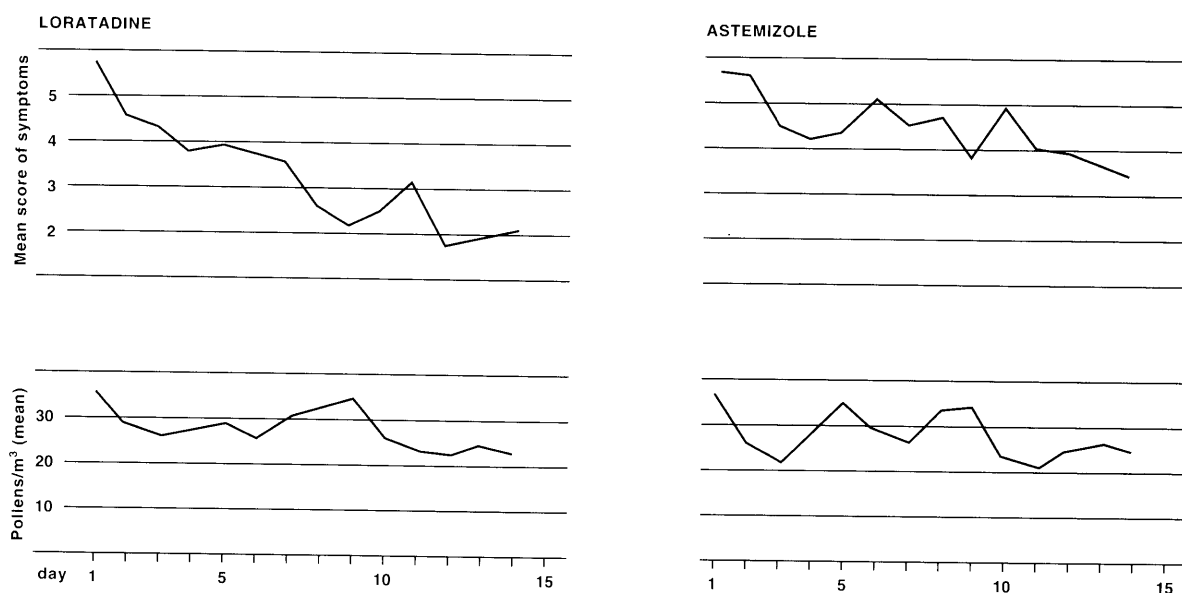


Fig. 2. Severity of symptoms, as assessed by patient/parent and its relationship with pollen count.

Results

Of the 41 children selected, 21 (mean age 8.45 ± 2.58 years) received loratadine and 20 (mean age 8.50 ± 2.76 years) received astemizole. Mean body-weights were 29.8 ± 8.4 and 27.4 ± 8.5 , respectively. Mean duration of allergic condition was 3.57 ± 1.99 years in the loratadine group, and 3.15 ± 1.53 years in the astemizole group. Patient distribution between the two treatment groups was essentially equal, and the two groups were comparable in terms of age, sex, body-weight, severity of symptoms and duration of disease. Three patients from both groups failed to attend a control visit during the study and were excluded from the evaluation. After the third day of treatment the mean ocular and nasal score of symptoms and signs was significantly lower ($p < 0.01$) than at baseline with no statistical difference between the two groups. The severity of symptoms improved with both drugs ($p < 0.01$) during the 14-day treatment period both in terms of subjective symptoms and on physical examination. The assessments made independently by the investigators (Fig. 1) and the patients or their parents (Fig. 2) showed an equivalent trend.

Although not statistically significant, the improvement of nasal symptoms in the loratadine-treated group was greater than in the astemizole group (Fig. 1). However, on day 7, nasal itching was better controlled ($p < 0.05$) by loratadine treatment. There was an equivalent improvement in ocular symptoms in both the loratadine- and astemizole-treated groups (Fig. 1). Symptom scores derived from patient diaries paralleled physician scores.

Rhinoscopy showed no statistically significant dif-

ference between the two treatments, both being associated with a significant reduction in nasal secretion.

As concerns the therapeutic response, excellent/good results were reported in the investigators' assessment for 83.3% of loratadine-treated patients and in 58.8% of patients treated with astemizole. A moderate/poor response was observed in 16.7% and 40.2% of patients, respectively. Comparable results were reported by patients/parents (Fig. 3). Adverse experiences were reported by nine children in the astemizole group and four in the loratadine group.

Three of the children in the astemizole group stopped the treatment due to side effects before the end of the study: one because of vomiting, one because of sedation, and one because of flushing malaise, paleness and mild urticaria 1 week after the start of treatment. Two other children complained of epistaxis, two showed flushing to face and legs, and two mild irritability.

In the loratadine group, four children reported, respectively, sedation, mild urticaria, restlessness and epistaxis. However, no patient stopped the treatment.

No significant trend towards any abnormality in laboratory parameters could be observed. More specifically, at the dosages used, both loratadine and astemizole were devoid of toxic effects measured in terms of electrolyte balance, liver and kidney function, or haematologically.

Discussion

Our children received randomized treatments but the double-blind technique was not used. This may

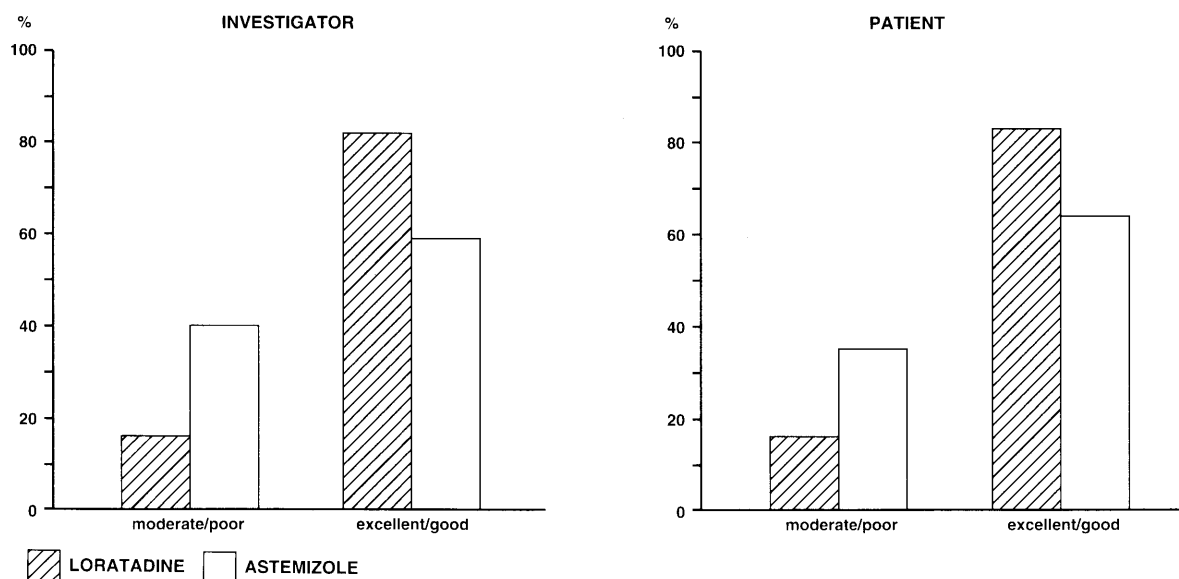


Fig. 3. Therapeutic response to the treatments in the assessment of both the investigator and patient/parent.

be acceptable in children when a drug is new (7). However, we were careful to prevent the evaluators from knowing the treatment regimen. The results of this study suggest that loratadine is as effective as astemizole in the treatment of allergic rhinoconjunctivitis in children.

Substantial improvement in allergy symptoms was observed by the first evaluation (day 3 of treatment) with both drugs. This is rather surprising for the astemizole-treated group since it is well known that this drug has a somewhat gradual and slow onset of action (4). For example, it has been shown that there is a lag of 5 days after initiation of therapy before treatment benefit becomes statistically significant in comparison with placebo in patients with seasonal allergic rhinitis (5). Thus, when a rapid effect is desired, a loading dose must be administered (10). This was not adopted in our study and so the rapid effect needs to be explained differently. Day-by-day evaluation of the pollen count for specific antigens for every single patient showed reduced pollen exposure during the first days of treatment in the astemizole-treated group, and so a reduced stimulus might account for the rapid onset of drug action (Fig. 2).

We have previously observed that the ability of loratadine to ameliorate hay fever symptoms in children is similar to that of dexchlorpheniramine (2). Dexchlorpheniramine, however, induces 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 those treated with dexchlorpheniramine (2).

In our study, the improvement in symptoms, particularly nasal symptoms, was better with loratadine than with astemizole, which is considered one of

the most effective non-sedative antihistamine compounds (10). Although astemizole is a potent H_1 blocker and devoid of sedative and anticholinergic side effects, it is not entirely free of disadvantages deriving from its long duration of action (4). Even if all of the side effects observed in our study cannot always be referred to the treatment regimen, our results suggest that loratadine treatment is associated with fewer side effects than those of astemizole treatment. Therefore, it can be concluded that a 2-week period of treatment with loratadine at a daily dose of 5 mg or 10 mg is effective and safe in children with allergic rhinoconjunctivitis. A longer period of study, through a whole pollen season, is necessary to confirm the persistence of positive effects, as already observed in adult patients (3).

Acknowledgement

The authors would like to thank Dr. Guido Marcer – Institute of Work Medicine of the University of Padova – for the results of the pollen count.

References

- BIERMAN CW, MONGAR JL. Antihistamines. In: YAFFE SJ, ed. Pediatric pharmacology. Therapeutic principles in practice New York: Grune & Stratton, 1980: 213–32.
- BONER AL, MIGLIORANZI P, RICHELLI C, MARCHESI E, ANDREOLI A. Efficacy and safety of loratadine suspension in the treatment of children with allergic rhinitis. *Allergy* 1989; 44: 437–41.
- BOUSQUET J, CHANAL I, SKASSA-BROCIK W, LEMONIER C, MICHEL FB. Lack of subsensitivity to loratadine during long-term dosing during 12 weeks. *J Allergy Clin Immunol* 1990; 86: 248–52.
- DROUIN MA. H_1 antihistamines: perspective on the use of the conventional and new agents. *Ann Allergy* 1985; 55: 742–52.

5. HOWART PH, EMANUEL MB, HOLGATE ST. Astemizole, a potent histamine H1 receptor antagonist: Effect in allergic rhinoconjunctivitis on antigen and histamine induced skin wheal responses and relationship to serum levels. *Br J Clin Pharmacol* 1984; 18: 1-8.
6. KREUTNER W, CHAPMAN RW, GULBENKIAN A, SIEGEL MI. Antiallergic activity of loratadine, a non-sedating antihistamine. *Allergy* 1987; 42: 57-63.
7. NICKOLAS A, SHEFFER AL, ADKINSON NF Jr. Workshop 3: study design. Report of the American Academy of Allergy and Clinical Immunology Task Force on guidelines for clinical investigation of non-bronchial antiasthmatic drugs. *Ann Allergy Clin Immunol* 1986; 78 (Suppl.): 507-17.
8. SIMONS FER. Loratadine, a non-sedating H1-receptor antagonist (antihistamine). *Ann Allergy*, 1989; 63: 266-8.
9. SIMONS FER, SIMONS KJ. H1-receptor antagonists: clinical pharmacology and use in allergic disease. *Pediatr Clin North Am* 1983; 30: 899-914.
10. VANDEN BUSSCHE G, EMANUEL MB, ROMBAUT N. Clinical profile of astemizole. A survey of 50 double-blind trials. *Ann Allergy* 1987; 58: 184-8.