

A Double-Blind, Placebo-Controlled, and Randomized Study of Loratadine (Clarityne) Syrup for the Treatment of Allergic Rhinitis in Children Aged 3 to 12 Years

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Prevalence of allergic rhinitis, the most common allergic disorder, has increased over the last three decades in several countries.¹ The pathogenesis of this disease has also been well studied. Briefly, interactions of allergens, antigen presenting cells, T lymphocytes and B lymphocytes induce the production of serum IgE. When antigens bind to IgE antibodies that occupy certain receptors (FcεRI) on mast cells, the mast cells degranulate, and then release inflammatory mediators such as platelet-activating factor, tryptase, histamine and so on.² Histamine, one of these mediators, is crucial in allergic rhinitis. Mediated by H1-receptors, histamine causes many effects including increased postcapillary venular permeability, increased release of other cytokines and enhanced mucus secretion.³

Loratadine, a once-daily antihistamine, with high specificity for the H1-receptor and a 24-hour duration of effect, lacks sedative or anticholinergic effect. It has been

SUMMARY Allergic rhinitis is a common disease in children, and antihistamines are the key medication. However, traditional tablets are not convenient and lead to low compliance in young children. The aim of this double-blind, placebo-controlled, parallel, randomized study was to evaluate the effectiveness and safety of loratadine syrup for the treatment of children aged 3 to 12 years with allergic rhinitis. Sixty children with allergic rhinitis due to dust mites were enrolled. They were randomized into 2 parallel groups: one group received loratadine syrup 5 mg or 10 mg daily for 3 weeks, and the other group received placebo. The patients returned to special clinics for symptoms evaluation at day 7 and day 21, and the parents were requested to record disease severity daily. Both evaluations, physician's and parents', were recorded with a 4-point scale for 5 symptoms: sneezing, rhinorrhea, nasal congestion, nasal itching and ocular symptoms. Forty-six patients completed the study, 22 in the loratadine group and 24 in the placebo group. At the initial visit, the total symptom score (TSS) in both groups was not significantly different ($p = 0.39$). The TSS of the loratadine syrup group at day 7 and day 21 was lower than those of the placebo group ($p = 0.003$, $p = 0.06$). The daily card scores in the experimental group were also significantly lower than those of the placebo group (week 1, $p = 0.014$; week 2, $p = 0.029$; week 3, $p = 0.014$). No adverse reactions were recorded in both groups. This study revealed that loratadine syrup 5 mg or 10 mg once a day improved symptom scores of children with allergic rhinitis effectively and safely.

commonly used in the treatment of disorders like urticaria or allergic rhinitis which are induced mainly by histamine.^{4,5} Loratadine syrup is one representation of the drug designed for younger children.⁶ In this 3-week clinical study, we evaluated the efficacy, safety, and drug

compliance of loratadine syrup for childhood allergic rhinitis.

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MATERIALS AND METHODS

Patients

Sixty Chinese children, 3 to 12 years of age, with a history of allergic rhinitis due to house dust mites were recruited. They were randomized into 2 groups: thirty patients were included in the study group receiving loratadine and the other 30 patients received placebo and acted as the control group. All children had at least 3 of the 5 following symptoms at enrollment: sneezing, rhinorrhea, nasal congestion, nasal itching and ocular symptoms. These 5 symptoms were graded on a 4-point scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe). Patients had to be symptomatic with a total symptom score equal or greater than 7. Sensitivity to dust mites was confirmed by positive skin prick test and/or a positive CAP (Pharmacia & Upjohn, Sweden) result to *Dermatophagoides pteronyssinus* or *Dermatophagoides farinae*. Exclusion criteria were diseases that might interfere with the study outcome or require specific treatment (such as severe asthma, severe atopic dermatitis, heart failure, renal or hepatic dysfunction). Patients were excluded from the study, if they had a known idiosyncratic reaction to antihistamines, or a history of multiple drug allergies. Also excluded were patients who received drugs before the enrollment, including ketotifen within 2 weeks, 2nd generation antihistamines within 4 weeks, short acting antihistamines within 4 days, systemic corticosteroid within 2 months, intranasal or eye drops containing a corticosteroid within 2 weeks, anticholinergics within 2 days, topical cromoglycate within one week, and nasal decongestant within 2 days. Informed consent of all subjects was obtained from their parents, and the study was ap-

proved by the ethics committee of the National Taiwan University Hospital.

Drug administration

All patients were randomly assigned to receive either loratadine syrup (1 mg/ml) or placebo for 3 weeks. The doses were adjusted according to body weights. Patients received the drug at a dose of 5 mg once daily if the body weight was less than 30 kg, or 10 mg once daily if the body weight was equal to or more than 30 kg. The medications were returned to the investigators at each visit to check the compliance by the remaining content in the bottle.

Evaluation of efficacy and side effects

After the initial evaluation (visit I), all patients visited the special clinics at day 7 (visit II) and day 21 (visit III). At each visit, the investigators reevaluated the five cardinal symptoms of allergic rhinitis. Adverse experiences were questioned and recorded. Patients' parents were given diary cards for daily recording of the five symptoms, using the previous described 4-point scoring system. These assessments had to be made at the

same time of the day, preferably in the evening.

Statistical analysis

The characteristics of both groups were compared by Fisher's Exact test for categorical variables and Mann-Whitney test for quantitative variables. Efficacy measurements include total symptom score (TSS) for allergic rhinitis that derived from the diary cards and from the investigators. The comparison between the two groups was evaluated by Mann-Whitney test. A two-tailed *p* value of less than 0.05 was considered statistically significant.

RESULTS

Patient demographics

Sixty children were enrolled in this study. Among them, 46 patients completed this 3-week clinical trial (22 in the loratadine syrup group; 24 in the placebo group). The characteristics of the two treatment groups are shown in Table 1. Overall, 26 (57%) patients were males and 20 (43%) patients were females. There were no significant differences between both groups with regards to age, body weight, body height, and sex.

Table 1 Demographics of patients with allergic rhinitis

	Loratadine syrup (N = 22)	Placebo (N = 24)	<i>p</i> -value
Age (years)	6.0 ± 2.7	6.6 ± 2.5	0.388
Height (cm)	113.2 ± 25.0	110.0 ± 19.5	0.795
Weight (kg)	23.6 ± 8.0	25.5 ± 8.7	0.372
Sex (%)			0.388
Male	63.6	50.0	
Female	36.4	50.0	

Values were presented as mean ± SD and compared by Fisher's Exact test for categorical variables and Mann-Whitney test for quantitative variables

Efficacy evaluation

The efficacy of loratadine syrup for these 5 symptoms was evaluated by comparing the last week (day 15-day 21) symptom scores from the diary cards between the two groups (Fig. 1). The symptoms of rhinorrhea and sneezing in the loratadine syrup group improved significantly when compared with the placebo group ($p = 0.009$, $p = 0.004$). The scores for nasal itching and nasal stuffiness in the loratadine syrup group were also lower than in the placebo group, although not statistically significant ($p = 0.07$, $p = 0.08$). Loratadine syrup seemed not to be very effective in relieving ocular symptoms of childhood allergic rhinitis ($p = 0.224$).

Table 2 shows that the TSS between the two groups at visit I was not statistically different. At visit II and visit III, the TSS for patients in the loratadine syrup

group were 4.6 ± 3.3 and 5.2 ± 3.5 , weekly (Table 2), and showed that the score in the loratadine syrup group was significantly lower than in the placebo group ($p = 0.014$ in the first week, $p = 0.029$ in the second week, $p = 0.014$ in the third week).

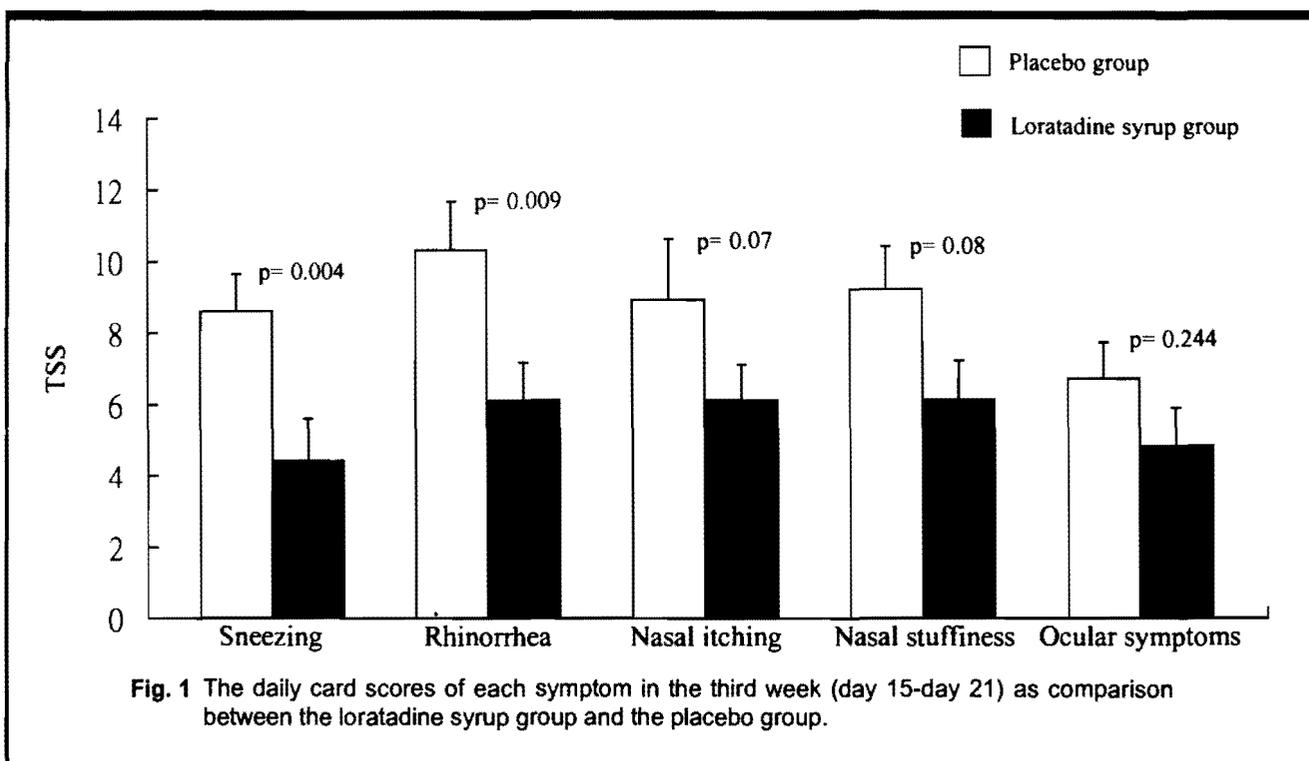
Compliance and adverse effects

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Table 2 Comparison of total symptom score (TSS) between the loratadine syrup group and the placebo group at each visit and that of daily cards in each week

	Loratadine syrup (N = 22)	Placebo (N = 24)	p-value
Visit I	9.0 ± 1.1	8.8 ± 1.4	0.389
Visit II	4.6 ± 3.3	7.5 ± 3.2	0.003
Visit III	5.2 ± 3.5	6.8 ± 2.6	0.063
Week 1	31.8 ± 19.2	46.3 ± 20.4	0.014
Week 2	30.4 ± 19.3	45.0 ± 22.3	0.029
Week 3	27.6 ± 22.3	43.7 ± 22.4	0.014

Values were presented as mean \pm SD and compared by Mann-Whitney test



amount of drug at each visit, it was found that all 46 patients took the syrup in the recommended doses regularly. Only one of 14 patients who did not complete the study complained about an unpleasant taste of the syrup. No adverse event was recorded for either the loratadine syrup or the placebo group during this 3-week study period.

DISCUSSION

In this double-blind, placebo-controlled, and randomized study, we demonstrated clearly that loratadine syrup, 5 mg or 10 mg once daily, was effective and well tolerated for Chinese children aged 3 to 12 years suffering from allergic rhinitis during the 3-week therapeutic period. Allergic rhinitis is a chronic nasal inflammatory disease, induced by allergens such as dust mites and pollen. In Taiwan, the prevalence of allergic rhinitis increased yearly not only in adults but also in children.^{7,8} Although allergic rhinitis is not a life-threatening disorder, it is often complicated with paranasal sinusitis and/or otitis media if not well treated.⁹ Besides, it is a major cause of restricted activity and loss of productivity at work and school.¹⁰ The first task to control allergic rhinitis is to avoid contact with the allergens. However, airborne allergens like dust mites are difficult to be avoided entirely. Aggressive medical intervention is necessary when the disease develops.

Loratadine, a selective peripheral H₁-receptor antagonist, is well documented and widely used for both adults and children over than 6 years old with allergic rhinitis.⁴ In our clinical practice, the traditional loratadine tablet (10 mg) is associated with a poor compliance in children, especially in pre-

school children. The syrup form of the drug is more convenient and acceptable for young children.⁶ This study revealed that loratadine syrup for children containing the same active agents as the tablet form for adults, was effective and safe for the treatment of the symptoms of allergic rhinitis.

According to the results of the TSS of physician's records and daily cards in this study, under loratadine syrup treatment, childhood allergic rhinitis improved significantly within one week, and the improvement persisted until the end of the trial. Sneezing, rhinorrhea, nasal stuffiness, and nasal itching were typical symptoms of allergic rhinitis. Besides these, allergic conjunctivitis with ocular itching, erythematous change of the conjunctiva and increased secretion develops commonly in patients with allergic rhinitis.¹¹ Loratadine syrup was effective to relieve the symptoms of sneezing and rhinorrhea, and also seemed to have some effects on nasal itching and stuffiness. Without local anti-inflammatory drug or local anti-histamine,¹² loratadine syrup alone did not control ocular symptoms effectively in our study.

Although previous literatures had revealed the efficacy and safety of loratadine in young children,^{5,6} to our best knowledge, this was the first double-blind, placebo-controlled clinical study of loratadine syrup treatment of Asian children with allergic rhinitis. Besides, this study also discussed and showed the effectiveness of this drug for each individual symptom of allergic rhinitis. In conclusion, histamine plays a key role in allergic reactions of the nose.³ Antihistamines, especially second-generation non-sedative antihistamines are therefore im-

portant in the treatment of allergic rhinitis. Loratadine syrup, 5 mg or 10 mg daily, provides a new option of treatment for little children with allergic rhinitis without significant side effects.

ACKNOWLEDGMENTS

We thank Schering-Plough to support this clinical study.

REFERENCES

1. Asher MI, Keil U, Anderson HR, *et al.* Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, atopic dermatitis: ISAAC. *Lancet* 1998; 351: 1225-32.
2. Stites DP, Terr AI, Parslow TG. *Medical immunology*. 9th edition, Appleton & Lange, 1997; 377-8.
3. White MV. The role of histamine in allergic diseases. *J Allergy Clin Immunol* 1990; 86: 599-605.
4. Dockhorn RJ, Bergner A, Connell JT, Falliers CJ, Grabiec SV, Weiler JM, *et al.* Safety and efficacy of loratadine (Sch-29851): a new non-sedating antihistamine in seasonal allergic rhinitis. *Ann Allergy* 1987; 58: 407-11.
5. Salmun LM, Herron JM, Banfield C, Padhdi D, Lorber R, Affrime MB. The pharmacokinetics, electrocardiographic effects, and tolerability of loratadine syrup in children aged 2 to 5 years. *Clin Ther* 2000; 22: 613-21.
6. Boner AL, Miglioranza 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.
7. Li LF, Lin MC, Yang CT, Hiesh MJ, Huang CC, See LC, Tsao TC. Comparison of indoor allergens, allergic scores, and demographic data in Taiwanese adults with asthma or allergic rhinitis, or both. *J Formos Med Assoc* 1999; 98: 486-91.
8. Wang WC, Leu KH, Sheu JN. Allergic diseases in pre-school children in Taichung city. *Acta Paediatr Taiwan* 1998; 39: 314-8.
9. Skoner DP. Complications of allergic rhinitis. *J Allergy Clin Immunol* 2000; 105: s605-9.
10. Horak F, Toth J, Marks B, Stubner UP, Berger UE, Jager S, Burtin B, Duby C. Efficacy and safety relative to placebo

- of oral formation of cetirizine and sustained-released pseudoephedrine in the management of nasal congestion. *Allergy* 1998; 53: 849-56.
11. Schneider LC, Lester MR. Atopic disease, rhinitis and conjunctivitis, and upper respiratory infections. *Curr Opin Pediatr* 1998; 10: 539-47.
12. Lanier BQ, Gross RD, Marks BB, Cockrum PC, Juniper EF. Olopatadine ophthalmic solution adjunctive to loratadine compared with loratadine alone in patients with active seasonal allergic conjunctivitis symptoms. *Ann Allergy Asthma Immunol* 2001; 86: 641-8.