Prevention of Recurrent Wheezing in Young Children by Loratadine Compared with Ketotifen

Jarungchit Ngamphaiboon MD*,
Thiwan Wirawarn MD**, Thaneeya Thongkaew RN*

** Department of Pediatric, Allergy and Immunology Unit, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand*
*** Department of Pediatric, Thainakarin Hospital, Bangkok, Thailand*

Background: *Various trials showed benefit of the prophylactic agent ketotifen in prevention of recurrent wheezing in young children, but no such clinical trial with loratadine or comparison trial is available.*
Objective: *To study the efficacy and safety of loratadine syrup compared with ketotifen and placebo in prevention of recurrent wheezing in young children.*
Material and Method: *Randomized double-blind placebo controlled trial on 90 recurrent wheezing children aged less than 6 years old was done. Children were randomized to receive loratadine, ketotifen syrup, or placebo with dose of 0.25cc/kg once a day for four months. Blood biochemistry (CBC, LFT) and EKG were performed pre and post treatment period. Assessment of symptoms-wheezing and night cough including use of bronchodilators was done daily via patient diary card. Subjects were asked to do monthly visits to the clinic for physical examination. At those visits, the doctors questioned the patients about adverse event.*
Result: *Of the 90 children enrolled, 12 dropped out. Thus, 27 children remained in the loratadine, 26 in the placebo, and 25 in the ketotifen group. The demographic data were comparable among the three treatment groups. It was noted that wheezing decreased significantly at 2 months in the ketotifen ($p = 0.008$) and at 3 months in the loratadine ($p = 0.029$) but not in the placebo group. Coughing at night decreased significantly at 3 months in both the loratadine ($p = 0.005$) and the ketotifen ($p = 0.036$) group. The use of bronchodilator drug was significantly decreased at 2 months in the ketotifen ($p = 0.028$) and placebo ($p = 0.025$) group, and at 3 months in the loratadine ($p = 0.009$) group. Only a few patients had mild adverse events in all groups.*
Conclusion: *Loratadine and ketotifen are safe and effective significantly in prevention of recurrent wheezing in young children.*

Keywords: *Recurrent wheezing, Children, Loratadine, Ketotifen*

J Med Assoc Thai 2009; 92 (3): 351-5
Full text. e-Journal: *http://www.mat.or.th/journal*

Wheezing in young children is a common and challenging problem. Its prevalence varies world widely between 4% and 32%[1]. Symptom is common due to anatomy and physiology of airway system of children at this age including many other unknown factors. Evaluation of infants with persistent or recurrent wheezing then needs a comprehensive assessment of a thorough clinical history, physical examination, and appropriate diagnostic laboratory tests. Taussing LM et al[2] in 1980 conducted Tucson Children's Respiratory Study (TCRS) with the aim to determine risk factors of acute lower respiratory disease and chronic lung disorder especially asthma during childhood and early adult life. TCRS observed 1,246 subjects from birth and 974 (78%) in cohort were followed up for 22 years. Three different types of wheezing disorder: transient, non-atopic, and atopic were described from the study. In another wheezing study among children aged 0-6 years old by Martinez et al[3], prevalence of transient wheeze (at least one wheezing with respiratory infection at the age of 3 years old) was 20% and 59% of transient

Correspondence to: Ngamphaiboon J, Faculty of Medicine, Department of pediatric, Chulalongkorn University, 1873 Rama IV Rd, Patumwan, Bangkok 10330, Thailand. Phone: 0-2256-4933, Fax: 662-256-4911, E-mail: ngamphaiboon_j @yahoo.com

wheeze stopped wheezing at the age of 6. Whereas prevalence of late wheeze (started wheezing at 6 years of age) and of persistent wheeze (wheezing started before 3 years old and continued to the age of 6) was 15% and 13.7%, respectively.

Various trials showed benefit of a prophylactic agent, ketotifen, in the prevention of recurrent wheezing in young children. For example, Y likura et al[4] evaluated the prophylactic effect of ketotifen against the onset of asthma in 121 infants with atopic dermatitis who had no history suggestive of asthma for one year. Asthma was significantly less in ketotifen (13.1%) than placebo (41.6%) group ($p < 0.001$). Loratadine is a non-sedating antihistamine that is indicated for the relief of seasonal rhinitis. Recently Grimfeld A et al[5] demonstrated the efficacy and long-term safety of loratadine in preventing the onset of respiratory exacerbations in 412 children aged 12-30 months old. However, comparative study in prevention of recurrent wheezing in young children between ketotifen and loratadine is quite few. The present study aimed to evaluate the efficacy and safety of loratadine syrup compared with ketotifen and placebo in the prevention of recurrent wheezing in young children.

Material and Method

The present study was a randomized double-blind placebo controlled trial with inclusion criteria of age under 6 years old, having a positive history of recurrent wheezing bronchitis more than three times in the past year, normal chest x-ray, no other chronic diseases and no prior and concomitant medications as follows:

Medication restriction	Time limit prior to screening
Inhaled corticosteroid	never permitted
Sodium cromoglycate	never permitted
Oral, injected corticosteroid	4 weeks
Short acting antihistamine	12 hrs
Long acting antihistamine	7 days

Exclusion criteria were a child over 6 years old, need of ICS and/or sodium cromoglycate during the present study, on loratadine or ketotifen 30 days before the present study, prior received immunotherapy, abnormal blood biochemistry, abnormal EKG and sensitive to loratadine or ketotifen or any of their ingredients.

All eligible children were randomized to receive either loratadine or ketotifen syrup, or placebo with the dose of 0.25cc per kg body weight once a day for four months. Bronchodilator drugs were allowed to continue during the present study as required. Blood biochemistry (CBC, LFT) and EKG were performed both pre- and post-treatment periods. During treatment, subjects were asked to visit the clinic at one-month interval for physical examination and to assess adverse events. Symptom assessment including frequency of wheezing and cough as well as frequency of bronchodilator used was done via the patients' daily record by the subjects' parents. All subjects' parents were instructed on how to fill the symptom diary card. At each month of clinical visit, they would return the filled forms and collect the new one. Since there was no information before treatment, information after the first month of treatment was used as baseline data for comparison. Frequency data of wheezing, cough, and use of bronchodilator drugs were tabulated and calculated as mean for each month. Paired t-test was used for statistical analysis to compare mean of each symptom/bronchodilator drugs use between each study interval within its treatment group. A p-value of less than 0.05 was considered statistically significant. Written informed consent was obtained from parents whose children were recruited. The present study was approved by the Research Ethics Committee of the Faculty of Medicine, Chulalongkorn University.

Results

Of the 90 children enrolled, 12 dropped out during the present study. Analysis was mainly based on 78 subjects completing the present study (27 in loratadine, 26 in placebo, and 25 in ketotifen group). All treatment groups had similar demographic data such as sex, age, weight, height, and family history of allergy (Table 1).

Table 1. Demographic data (n = 78) of subjects among three different treatment groups

	Loratadine (n = 27)	Placebo (n = 26)	Ketotifen (n = 25)
Sex			
Male	19	17	12
Female	8	9	13
Age (yrs)			
Mean (SD)	3.2 (1.31)	2.9 (1.33)	2.9 (1.18)
Height (cm)			
Mean (SD)	96.4 (10.36)	91.8 (11.18)	94.6 (11.44)
Weight (kg)			
Mean (SD)	13.9 (3.3)	14 (3.49)	14.8 (4.54)
Family history of allergy			
Yes	17	18	16
No	10	8	9

From the patients' diary records, mean of wheezing frequency per month (3.64) in the ketotifen group after one month of treatment was significantly decreased to 0.56 at month 2 ($p = 0.008$). For the loratadine group, wheezing symptom was significantly decreased at month 3 of treatment (2.41 vs. 0.81) ($p = 0.028$). No significant change in wheeze was found in the placebo group (3.04 vs. 1.48) ($p = 0.88$) (Fig. 1).

Compared with the severity of coughing at month 1 the severity of coughing at night was decreased significantly at month 3 of treatment both in the loratadine (11.67 vs. 6.12) ($p = 0.005$) and ketotifen groups (15.88 vs. 9.68) ($p = 0.036$) until month 4. In placebo group, the severity of coughing at night was decreased significantly at month 2 and month 3 of treatment (12.12 vs. 7.12) ($p = 0.046$) but not significantly at month 4 ($p = 0.077$), so it might be from the placebo effect (Fig. 2).

Fig. 3 shows frequency use of bronchodilator drug during the present study among the treatment group. It was noted that use of bronchodilator drug was decreased significantly in all treatment groups. At month 2, use of bronchodilators in the ketotifen group was significantly reduced from 15.04 times/month to 10.16 times/month ($p = 0.028$) as well as the placebo group from 10.2 to 6.19 ($p = 0.025$). Similarly, use of bronchodilators was significantly decreased from 8.81 times/month to 4.19 times/month ($p = 0.009$) for the loratadine group at month 3 until month 4 in all treatment groups. In both active treatment groups, the use of bronchodilators was significantly reduced proportionately to the symptoms, even wheezing and coughing at night. However, in the placebo group it was not correlated. It may have been an error not to record after taking, during the symptoms.

No abnormal test results in blood chemistry, EKG, and X-ray were found among the three treatment group after four months of treatment. Few patients had mild adverse events in all groups such as irritability and somnolence.

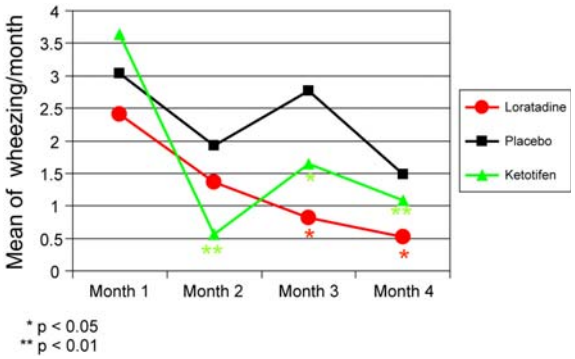

Fig. 1 Comparison of wheezing among three different groups

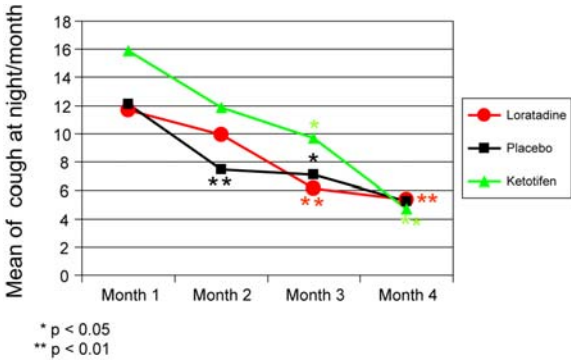

Fig. 2 Comparison of night cough among three different groups

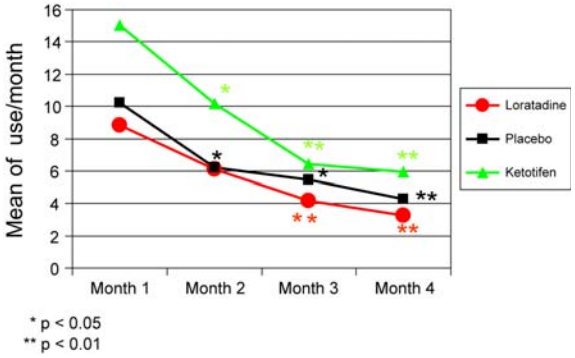

Fig. 3 Comparison of bronchodilator drug used among three different groups

Discussion

The present study demonstrated that loratadine is safe and effective in the prevention of recurrent wheezing in young children as well as ketotifen after a few months of treatment. It also significantly reduced symptom of night cough and frequency of using bronchodilator drugs after 2-3 months of therapy. Ketotifen is considered an orally active prophylactic agent for the management of bronchial asthma and allergic disorders[6]. This is because of its antihistaminic property and strong anti-anaphylactic activity[7].

Efficacy of loratadine in preventing wheezing is mainly due to its pharmacological effect on inhibition

of the release of various inflammatory mediators including histamine[8,9]. Loratadine also decreases the expression of intercellular adhesion molecule type 1 (ICAM-1) on the surface of epithelial cells[10-12]. Patho-physiological studies confirmed that reduction of inflammatory mediators such as cytokine production[13,14] and down regulation of ICAM-1[15,16] would prevent non-specific airway inflammation leading to wheezing prevention. Grimfeld A et al[5] evaluated the efficacy and long-term safety of loratadine in reducing the number of respiratory infections and the benefit of loratadine treatment in preventing the onset of respiratory exacerbations in 412 children aged 12-30 months old for 24 months of treatment. Statistically significant effect of loratadine was observed on less number of respiratory exacerbations in patients who experienced wheezing during the treatment period ($p = 0.0497$). This is because loratadine is not associated with any sedative effect[14] or risk of cardiovascular events[17]. In the present study only a few patients had mild adverse events in all groups such as irritability and somnolence. Therefore, loratadine was safe to use in young children in preventing recurrent wheezing.

Conclusion

Loratadine and ketotifen are safe and effective in the prevention of recurrent wheezing in young children.

References

1. Worldwide variation in the prevalence of asthma symptoms: the International Study of Asthma and Allergies in Childhood (ISAAC) Eur Respir J 1998; 12: 315-35.
2. Taussing LM, Wright AL, Holberg CJ, Halonen M, Morgan WJ, Martinez FD. Tucson Children's Respiratory Study: 1980 to present.J Allergy Clin Immunol 2003; 111: 661-75.
3. Martinez FD, Wright AL, Taussing LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. N Engl J Med 1995; 332: 133-8.
4. Iikura Y, Naspitz CK, Mikawa H et al. Prevention of asthma by ketotifen in infants with atopic dermatitis. Ann Allergy 1992; 68: 233-6.
5. Grimfeld A, Holgate ST, Canonica GW et al. Prophylactic management of children at risk for recurrent upper respiratory infections: the Preventia I Study. Clin Exp Allergy 2004; 34: 1665-72.
6. Craps LC, Greenwood C, Ney UM. Ketotifen and asthma. In: Weiss EB, Segal MS, Stein M, eds. Bronchial asthma. Boston:Little, Brown and Company. 1985: 734-40.
7. Naspitz CK, Tinkelman DG. Therapeutic approaches to the treatment of chronic asthma. New York:Marcel Dekker, 1987: 249-80.
8. Kreutner W, Chapman RW, Gulbenkian A, Siegel MI. Antiallergic activity of loratadine, a non-sedating antihistamine. Allergy 1987; 42:57-63.
9. Miadonna A, Milazzo N, Lorini M, Marchesi E, Tedeschi A. Inhibitory effect of the H1 antagonist loratadine on histamine release from human basophils. Int Arch Allergy Immunol 1994; 105: 12-7.
10. Vignola AM, Crampette L, Mondain M et al. Inhibitory activity of loratadine and descarboethoxy loratadine on expression of ICAM-1 and HLA-DR by nasal epithelial cells. Allergy 1995; 50: 200-3.
11. Ciprandi G, Catrullo A, Cerqueti P, Tosca M, Fiorino N, Canonica GW. Loratadine reduces the expression of ICAM-1. Allergy 1998; 53: 545-6.
12. Papai A, Papadopoulos NG, Stanciu LA, Degitz K, Holgate ST, Johnson SL. Effect of desloratadine and loratadine on rhinovirus-induced intercellular adhesion molecule 1 upregulation and promoter activation in respiratory epithelial cells. J Allergy Clin Immunol 2001; 108:221-8.
13. Anderson LJ, Tsou C, Potter C et al. Cytokine response to respiratory syncytial virus stimulation of human peripheral blood mononuclear cells. J Infect Dis 1994; 170: 1201-8.
14. Gern JE, Busse WW. The effects of rhinovirus infections on allergic airway responses. Am J Respir Crit Care Med 1995; 152: S40-5.
15. Canonica GW, Ciprandi G, Buscaglia S, Pesce G, Bagnasco M. Adhesion molecules of allergic inflammation: recent insights into their functional roles. Allergy 1994; 49: 135-41.
16. Papi A, Johnson SL. Respiratory epithelial cell expression of vascular cell adhesion molecule-l and its up-regulation by rhinovirus infection via NF-kappaB and GATA transcription factors. J Biol Chem 1992; 274: 30041-51.
17. Hey JA, del Prado M, Egan RW, Sherwood J, Kreutner W. Loratadine produces antihistamine activity without adverse CNS, ECG or cardiovascular effects in guinea pigs. Comparative studies with terfenadine and sedating antihistamines. Int Arch Allergy Immunol 1995; 107: 418-9.

การป้องกันการกลับมีเสียงหายใจหวีดในเด็กด้วยยาลอราตาดีนเปรียบเทียบกับคิโตติเฟน

จรุงจิตร์ งามไพบูลย์, ทิวรรก์ วีรวรรณ, ฐานียา ทองแก้ว

***ภูมิหลัง**: มีการศึกษาต่าง ๆ ที่แสดงถึงประโยชน์ของคีโตติเฟน ในการป้องกันการกลับมีเสียงหายใจหวีดในเด็กเล็ก สำหรับยาลอราตาดีนยังไม่มีการวิจัยทางคลินิก*

***วัตถุประสงค์**: รายงานนี้ศึกษาถึงประโยชน์และความปลอดภัยของยาลอราตาดีนชนิดน้ำเชื่อมในการป้องกันการกลับมีเสียงหายใจหวีดในเด็กเล็กเทียบกับยาหลอก*

***วัสดุและวิธีการ**: โดยศึกษาเป็นการทดลองแบบสุ่มโดยปกปิดสองทางใช้ยาหลอกเป็นยาควบคุมเปรียบเทียบในเด็กอายุน้อยกว่า 6 ปีที่มี การกลับมีเสียงหายใจหวีด จำนวน 90 คน แบ่งเป็น 3 กลุ่ม คือ กลุ่มลอราตาดีน, กลุ่มคีโตติเฟนชนิดน้ำเชื่อม และกลุ่มยาหลอกนาน 4 เดือน ทั้ง 3 กลุ่ม จะได้รับยาขยายหลอดลมเมื่อมีอาการ จดบันทึกอาการ, จำนวนวันที่มีอาการเสียงหายใจหวีด และไอตอนกลางคืน การใช้ยาขยายหลอดลมและผลข้างเคียง เจาะเลือดตรวจนับเม็ดเลือดและหน้าที่ตับ และตรวจคลื่นไฟฟ้าหัวใจก่อนและหลังการรักษา ติดตามและประเมินผลโดยแพทย์ทุกเดือน*

***ผลการศึกษา**: พบว่าผู้ป่วยทั้งหมด 90 คน 12 คน ออกจากการศึกษา เหลือ 27 คนในกลุ่ม ลอราตาดีน 26 คนในกลุ่มยาหลอก และ 25 คน ในกลุ่มคีโตติเฟน ข้อมูลพื้นฐานของทั้ง 3 กลุ่มไม่แตกต่างกัน พบว่า ผู้ป่วยมีอาการหอบกลางคืนลดลงอย่างมีนัยสำคัญในเดือนที่ 2 ในกลุ่ม คีโตติเฟน ($p = 0.008$) และเดือนที่ 3 ในกลุ่ม ลอราตาดีน ($p = 0.029$) แต่ไม่ลดลงในกลุ่มยาหลอก ผู้ป่วยมีอาการไอตอนกลางคืนลดลงอย่างมีนัยสำคัญใน เดือนที่ 3 ในทั้งสองกลุ่มที่ได้ยารักษาโดยในกลุ่ม ลอราตาดีน ($p = 0.005$) และ คีโตติเฟน ($p = 0.036$) นอกจากนี้การใช้ยาขยายหลอดลมก็ลดลงอย่างมีนัยสำคัญในเดือนที่ 2 ของกลุ่ม คีโตติเฟน ($p = 0.028$) และยาหลอก ($p = 0.025$) ส่วนลอราตาดีน ลดลงในเดือนที่ 3 ($p = 0.009$) พบอาการข้างเคียงในทุกกลุ่มเพียงเล็กน้อยซึ่งไม่รุนแรง*

***สรุป**: ลอราตาดีน เป็นยาที่ปลอดภัยและได้ผลในการป้องกันการกลับมีเสียงหายใจหวีดในเด็กดีเทียบเท่ายาคีโตติเฟน*