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The Efficacy and Safety of 30 mg Fexofenadine HCl bid in Pediatric Patients with Allergic Rhinitis

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SUMMARY Allergic rhinitis is one of the most common chronic disorders in children. It is also one of the most common causes of absence from school. This study reports on the efficacy and safety of a twice-daily oral dose of fexofenadine HCl 30 mg in Asian children aged 6-11 years diagnosed with seasonal or perennial allergic rhinitis. A total of 100 children with a history of allergic rhinitis for more than one year and a positive prick skin test response to at least one of the common aeroallergens in Thailand were enrolled in this multi-center, open-label, non comparative study. The severity of individual symptoms such as sneezing, rhinitis, etc. and adverse events were recorded in diary cards by the patients in form of scores as well as by the investigator at each visit. The total symptom score (TSS) with or without blocked nose at baseline, week 1 and week 2 was recorded. The TSS was defined as the sum of the individual symptom scores except for the nasal blockage score, as nasal blockage was not expected to respond to antihistamine treatment. Only patients with a total symptom score ≥ 6 were included in the study. There was a statistically significant improvement at $p < 0.01$ for the TSS with or without blocked nose and for each symptom score such as blocked nose, sneezing, rhinorrhea, itchy nose/palate and/or throat, and itchy/watery/red eyes from baseline to week 1 and week 2. Additionally, there was a statistically significant improvement between week 1 and week 2 for itchy nose/palate and/or throat and itchy/watery/red eyes* ($p < 0.05$). The Kappa measure of agreement was statistically significant at $p < 0.001$ between investigator's and patient's / parent's assessment, indicating the same degree of satisfaction with the overall effectiveness of the treatment. Fexofenadine 30 mg bid is effective in reducing the total symptom score of allergic rhinitis including blocked nose and is generally well tolerated. It is not cardiotoxic and is safe for pediatric patients as young as 6 years of age.

Allergic rhinitis is one of the most common chronic disorders in children. The prevalence ranges between 9-42% and tends to increase all over the world.[1] It is also one of the most common causes of absence from school. Children with untreated allergic symptoms exhibit a poorer learning ability than non-allergic children.[2] The efficacy of newer H1-receptor antagonists in relieving the troubling symptoms of seasonal allergic rhinitis (SAR) is well-established.[3] Fexofenadine is a selective histamine H1 receptor antagonist that dose not cross the blood brain barrier. It is the active acid metabolite of terfenadine and has been termed a third generation antihistamine.[4] Third generation antihistamines are devoid of cardiac toxicity and also lack the central effects of the first generation antihistamines that can cause sedation and impaired mental performance and cognitive function. A number of large multicenter, double-blind, randomized, placebo-controlled studies have evaluated the effect of fexofenadine in grass

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pollen- and ragweed pollen-induced seasonal allergic rhinitis.[5-8] These identify its significant benefit for relieving nasal itch, sneeze and rhinorrhea as well as for conjunctival itch and watering. There is a clear, although smaller, effect in relieving nasal obstruction.[9] Fexofenadine has been shown to effectively treat moderate to severe seasonal allergic rhinitis symptoms in people aged 12 years and older.[6-8] It has demonstrated a safety profile similar to that of a placebo in all preclinical and clinical studies conducted to date, even when administered at high doses or for extended periods (240 mg twice daily for 12 months).[6-8,10] Simon *et al.*[11] have shown that a single dose of 30 mg and 60 mg fexofenadine HCl is safe and well tolerated. Graft *et al*.[12] reported the pooled safety and tolerability results of two large double-blind randomized, placebo controlled, multicenter trials conducted in pediatric patients, age 6-11 years suffering from seasonal allergic rhinitis who were treated with fexofenadine HCl 15, 30 and 60 mg twice daily. This current report aims to assess the efficacy and safety of a twice daily dose of fexofenadine HCl 30 mg in Asian allergic rhinitis children aged 6-11 years.

PATIENTS AND METHODS

Patients

Patients aged 6-11 years, with a history of allergic rhinitis for more than one year and a positive prick skin test response (wheal diameter at least 3 mm greater than the diluent's within 15 minutes after skin prick) to at least one of the common aeroallergens in Thailand (mite, cockroach, grass, mold, dog, cat and kapok) were enrolled.

Patient inclusion was also based on symptom severity (nasal blockage, sneezing, rhinorrhea, itchy nose/palate and/or throat and itchy, watery, red eyes) as rated by the patients and the parents. Symptom severity was rated on a 0 to 4 scale (0 = absent, 4 = very severe). The total symptom score (TSS) was defined as the sum of the individual symptom scores except for the nasal blockage score, as nasal blockage was not expected to respond to antihistamine treatment. Only patients with a total symptom score ≥ 6 were included in the study. Patients were excluded if they experienced an upper respiratory tract infection within 30 days of study entry, clinically had vasomotor rhinitis, cardiovascular, hepatic or renal disorders, other major systemic diseases or drug abuse; or had been involved in another experimental drug protocol within the past four weeks or received immunotherapy. Concomitant medications were kept to a minimum during the study. Concurrent treatment with other oral antihistamines, and parenteral, oral or nasal corticosteroids were prohibited. Some rescue medications were permissible, including topical or oral sympathomimetics, and topical antihistamines.

Study design

A multicenter, open-label, non comparative study of 30 mg fexofenadine HCl given orally twice daily to patients aged 6-11 years, who had symptoms of allergic rhinitis for at least more than one year, was conducted. The study protocol was approved by the appropriate ethics committee of each center and written informed consent was obtained from the patients or parents before entry into the study. A washout period required from prior treatments as described in the exclusion criteria was followed by a two week treatment period. Patients were required to make a maximum of four visits at weekly intervals or three if no washout was required.

Efficacy was evaluated by recording all symptoms as scores and combining the total symptom scores as recorded in the diary cards with the assessment of the investigator at each visit. Safety was measured by adverse events reported in the diary cards or through direct contact with the investigator in case of a serious adverse event. Laboratory evaluations (liver function: total bilirubin, alkaline phosphatase, SGOT, SGPT; renal function: serum creatinine, blood urea nitrogen; electrocardiogram) were made at entry and at the final visit. Physical examination and vital signs were performed at each visit.

Statistical methods

Data from the study were separated before analysis, i.e. intention-to-treat and per actual protocol. Patient demographics of both groups were presented by descriptive statistics such as numbers and percentages for categorical data, i.e. sex, ethic origin as well as by the treatment a patient has received for

allergic rhinitis and by the mean ± standard error (SE) for continuous data, i.e. age, height, weight, and duration of allergic rhinitis.

For efficacy analysis the total symptom score (TSS), TSS without blocked nose and each symptom score such as blocked nose, sneezing, rhinorrhea, itchy nose/palate and/or throat, and itchy watery red eyes were considered. Between baseline, week 1 and week 2, these symptoms were evaluated by the Friedman test. The differences between baseline and week 1, baseline and week 2, and week 1 and week 2 were evaluated by the Wilcoxon singed-ranks test. In all tests, $p < 0.05$ and/or $p < 0.01$ were considered statistically significant.

Safety was measured by adverse events. Adverse events were descriptively summarized, and a comparison was made using the McNemar test between visit 2 and visit 3. Rescue medications were noted by the type of medication and frequency of use.

Finally the Kappa measure of agreement was used to evaluate the investigator's assessment and the patient's or parent's assessment of the overall effectiveness of the treatment.

RESULTS

Demographics

Of 100 patients intended-to-treat, 88 patients at 4 centers were eligible for analysis as shown in Table 1. There were 54 boys and 34 girls with a mean age of 8.7 ± 0.16 years and with a mean duration of allergic rhinitis of 3.26 ± 0.23 years. The mean height was 133.1 ± 1.09 cm and the mean weight 31.92 ± 1.11 kg 36.8% of all patients received medication for allergic rhinitis.

Efficacy

The percentages of each symptom score at baseline are shown in Fig. 1A. The majority of the symptoms at baseline were grade 2, except for itchy, watery/red eyes where it was only grade 1. Fig. 1B-1F show the distribution of each symptom score by severity at baseline, week 1 and week 2. Fig. 2 shows the TSS with or without blocked nose at baseline, week 1 and week 2. There was a statistically significant improvement ($p < 0.01$) for the TSS with or without blocked nose and for each symptom score such as blocked nose, sneezing, rhinorrhea, itchy nose/palate and/or throat, and itchy/watery/red eyes from baseline, to week 1 and week 2.

Additionally, there was a statistically significant improvement between week 1 and week 2 for itchy nose/palate and/or throat and itchy/watery/red eyes* ($p < 0.05$) as shown in Table 2. The Kappa measure of agreement (Table 3) was statistically significant at $p < 0.001$ between the investigator's and the patient's/parent's assessment, indicating the same degree of satisfaction with the overall effectiveness of the treatment.

Safety

No adverse event resulting in the discontinuation of the study was caused by the study medication. General adverse events were reported across the treatment period, the majority mild in intensity. There was no causal relationship between the incidence of these adverse events and the fexofenadine HCl treatment. Headache (regardless of causality) was the most frequently reported adverse event at 6.8% with mild intensity. There were no significant differences in the clinical laboratory parameters between baseline and week 2. There was also no clinically meaningful change in any electrocardiogram.

DISCUSSION

Allergic rhinitis adversely affects emotional well-being, social functions, impairs cognitive functions and decreases quality of life.[13] The chronic inflammation associated with allergic rhinitis can also

Table 1 Patients' demography

Variables	Mean ± SE	95% CI for mean	
		Lower	Upper
Age	8.75 ± 0.16	8.43	9.07
Height	133.10 ± 1.09	130.93	135.27
Weight	31.92 ± 1.11	29.71	34.13
Duration of AR (years)	3.26 ± 0.23	2.80	3.72

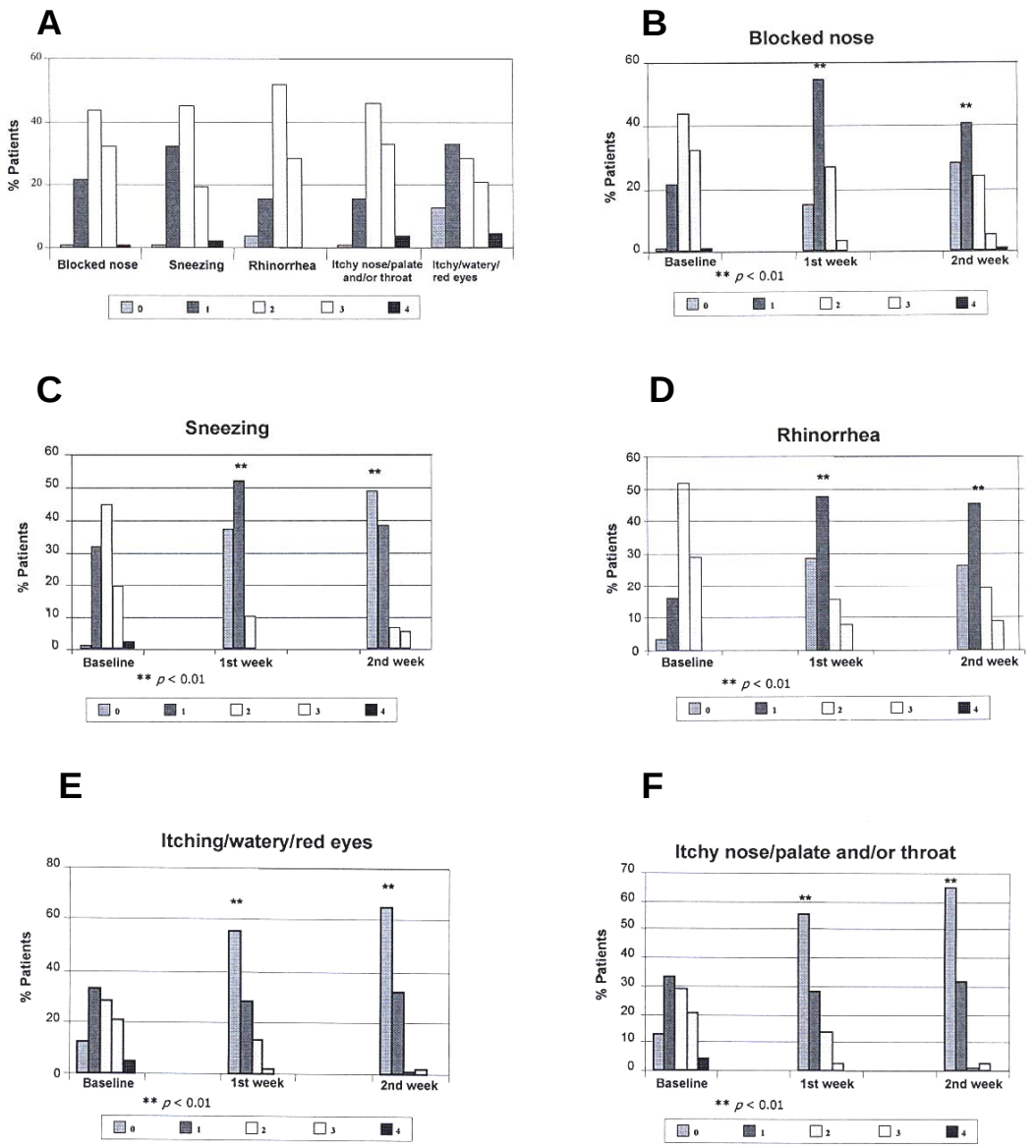

Fig. 1 A, The distribution of symptom scores of the patients at baseline; B, The distribution of symptom scores for blocked nose; C, The distribution of symptom scores for sneezing: D, The distribution of symptom scores for rhinorrhea; E, The distribution of symptom scores for itchy nose/palate and/or throat and F, The distribution of symptom scores for itching/watery/red eyes among baseline, week 1, and week 2, respectively.

predispose to chronic sinusitis or otitis media and an increased risk for asthma.[14-15] Therefore, a nonsedating and safe antihistamine that is effective in treating allergic symptoms is recommended. Hindmarck and Shamsi [16] performed a comprehensive review of published data from well controlled trials that evaluated effects of antihistamines on sedation, psychomotoric performance and cognition in healthy volunteers. They found that fexofenadine HCl was not associated with objective or subjective performance impairment

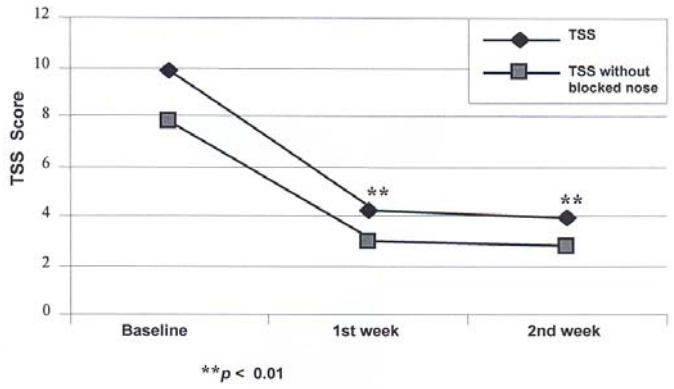

Fig. 2 The total symptom scores (TSS) at baseline, week 1, and week 2

Table 2 Wilcoxon Signed Ranks test between week 1 and baseline, week 2 and baseline, and week 2 and week 1 for each variable of TSS score

Variables	Week 1 & baseline	Week 2 & baseline	Week 2 & Week 1
Blocked nose	-6.445**	-6.506**	-0.964
Sneezing	-7.149**	-6.963**	-0.222
Rhinorrhea	-6.644**	-6.140**	-0.746
Itchy nose/palate and/or throat	-7.348**	-7.769**	-2.547*
Itchy watery red eyes	-6.334	-6.920**	-2.376*
TSS	-7.979	-7.951**	-1.501
TSS without blocked nose	-8.021**	-7.991**	-1.313

*p < 0.05, **p < 0.01

Table 3 The Distribution of investigator and patient or parent's assessment

Assessment	Investigator		Patient or parent	
	Number	%	Number	%
Poor	3	3.4	4	4.5
Good	50	56.9	46	52.3
Excellent	35	39.7	38	43.2

Measure of agreement Kappa = 0.556; p < 0.001

or cognitive impairment in any test even at higher than recommended doses when compared to loratadine and cetirizine.

This study shows that fexofenadine 30 mg bid causes a significant improvement in all allergic symptoms even nasal blockage, which is not usually obtained with oral antihistamines; these results concord with the Star Study.[17-20] An explanation for this could be that fexofenadine might have an anti-inflammatory property besides its antihistaminic property.[21] Regarding adverse effects and safety, we only found headache with mild intensity, but no causal relationship to the treatment as well as no

other serious adverse events. This correlates with other studies, also regarding the electrocardiogram where no effect of fexofenadine HCl on QTc was found.[12,22]

In conclusion, Fexofenadine 30 mg bid is effective in reducing the total score of allergic rhinitis including blocked nose and is generally well tolerated. It is not cardiotoxic and is safe for pediatric patients as young as 6 years of age.

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REFERENCES

1. Nathan RA, Meltzer EO, Selner JC *et al.* Prevalence of allergic rhinitis in the United States. J Allergy Clin Immunol 1997; 99: s808-14.
2. Vuurman ER, Van Veggel LM, Uiterwijk MM *et al*. Seasonal allergic rhinitis and antihistamine effects on children' learning. Ann Allergy 1993; 71: 121-6.
3. Simons FER. Histamine and H1-antihistamines in allergic disease. Marcel Dekker Inc, New York, 2002.
4. Handley DA, Magnetti A , Higgins AJ. Therapeutic advantages of third generation antihistamine. Expert Opin Invest Drug 1998; 7: 1045-54.
5. Howarth PH, Stern MA, Roi L *et al*. Double-blind, placebo controlled study comparing the efficacy and safety of fexofenadine hydrochloride (120 and 180 mg once daily) and cetirizine in seasonal allergic rhinitis. J Allergy Clin Immunol 1999; 104: 927-33.
6. Bronsky EA. Falliers CJ, Kaiser HB *et al.* Effectiveness and safety of fexofenadine, a new nonsedating H1-receptor antagonist, in the treatment of fall allergies. Allergy Asthma Proc 1998; 19: 135-41.
7. Bernstein DI, Schoenwetter WF, Nathan RA *et al*. Efficacy and safety of fexofenadine hydrochloride for treatment of seasonal allergic rhinitis. Ann Allergy Asthma Immunol 1997; 79: 443-8.
8. Casale TB, Andrade C, Qu R. Safety and efficacy of once daily fexofenadine HCl in the treatment of autumn seasonal allergic rhinitis. Allergy Asthma Proc 1999; 20: 193-8.
9. Van Cauwenberge P, Juniper EF. Comparison of the efficacy, safety and quality of life provided by fexofenadine HCl 120 mg, loratadine 10 mg and placebo administered once daily for the treatment of seasonal allergic rhinitis. Clin Exp Allergy 2000; 30: 891-9.
10. Mason J, Reynold R, Rao N. The systemic safety of fexofenadine HCl. Clin Exp Allergy 1999; 29 (Suppl): 163-73.
11. Simons FE, Bergman JN, Watson WT *et al*. The clinical pharmacology of fexofenadine in children. J Allergy Clin Immunol 1996; 88:1062-4.
12. Graft DF, Bernstein DI, Goldsobel A *et al.* Safety of fexofenadine in children treated for seasonal allergic rhinitis. Ann Allergy Asthma Immunol 2001; 87: 22-6.
13. Simon FER. Learning impairment in allergic rhinitis. Allergy Asthma Proc 1996; 17: 185-9.
14. Fuiman P. Treatment strategies designed to minimize medical complications of allergic rhinitis. Am J Rhinol 1997; 11: 95-102.
15. Greisner WA 3rd, Settipane RJ, Settipane GA. Co-existence of asthma and allergic rhinitis; a 23 year follow-up study of college students. Allergy Asthma Proc 1998; 19: 185-8.
16. Hindmarch I. Shamsi Z. Antihistamines: model to access the sedative properties, assessment of sedation, safety and other side effects. Clin Exp Allergy 1999; 29 (Suppl): 133-42.
17. Howarth PH, Wilson S, Lau L *et al*. The nasal mast cell and rhinitis. Clin Exp Allergy 1991; 21: 3-8.
18. Kemp JP, Buckley CE, Gershwin ME *et al.* Multicenter, double blind, placebo-controlled trial of terfenadine in seasonal allergic rhinitis and conjunctivitis. Ann Allergy 1985; 54: 502-9.
19. Clissold SP, Sorkin EM, Goa KL. Loratadine. A preliminary review of its pharmacodynamic properties and therapeutic efficacy. Drugs 1989; 37: 42-57.
20. Wahn U,Meltzer EO, Finn AF *et al*. Fexofenadine is efficacious and safe in children (aged 6-11 years) with seasonal allergic rhinitis. J. Allergy Clin Immunol 2003; 111: 763-9.
21. de Paulis A, Dente V, Onorati AM *et al*. Fexofenadine inhibits the release of mediators and IL-4 from human FcεRI+ cells. Allergy 1999; 54 (Suppl): 144 (Abstract p278).
22. Pratt CM, Mason J, Russell T *et al.* Cardiovascular safety of fexofenadine HCl. Am J Cardiol 1999; 83: 1451-4.