

A Non-Comparative Trial of the Efficacy and Safety of Fexofenadine for Treatment of Perennial Allergic Rhinitis

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After the second generation antihistamines have been introduced for treating allergic diseases in 1980, they have become widely used rapidly because of the advantage of being less sedative than the first generation ones. The more specific action to H₁ receptors of the drugs also results in negligible anticholinergic action. Since 1988, however, there were several reports of cardiac toxicity associated with the use of some second generation antihistamines.¹⁻⁵ This has led to an extensive study of the cardiac actions of the H₁ antihistamines and it is now accepted that some antihistamines, of both the first and second groups, under certain clinical conditions or in combination with some drugs, can cause prolonged QT interval and ventricular arrhythmias.^{6,7} Therefore, new H₁ antihistamines which are free from cardiac effects are urgently needed and in order to develop such antihistamines, the mechanism underlying the cardiotoxicity of antihistamines have been thoroughly investigated.⁸

At present, fexofenadine

SUMMARY An open-label, non-comparative study was performed in three Otolaryngology centers in Bangkok, Thailand, to assess the efficacy, safety and tolerability of fexofenadine in Thai patients with perennial allergic rhinitis. Altogether 101 perennial allergic rhinitis patients were included, 33 males and 68 females. Mean age was 33 years, average duration of symptoms was 6 years. All patients received fexofenadine hydrochloride 120 mg once daily (OD) in the morning for 2 weeks. Patients recorded their allergy symptoms daily using a 5 point rating scales in the diary card. At the end of 2 weeks, patients and investigators assessed the overall efficacy of treatment. Adverse events and onset of symptom relief were also recorded by every patient. Blood test and ECG were performed before and after treatment in one center (Siriraj Hospital). Total symptom scores and nasal scores decreased significantly from a baseline at 1 week and 2 weeks after treatment ($p < 0.05$). The mean onset of symptom relief was 2 hours and 12 minutes. The global assessment of the treatment by patients and investigators showed significant concordance. There was no significant change in either the vital signs, laboratory tests or ECG. The incidence of treatment related adverse events was 8% but all were mild and easily tolerated. Drowsiness was reported from only one patient. This study suggests that fexofenadine 120 mg once daily was an effective, safe and well tolerated treatment for perennial allergic rhinitis in Thai patients.

HCl, which is the active metabolite of terfenadine, has been developed and proved to be a potent H₁ antagonist⁹⁻¹¹ while having no significant cardiovascular effect.¹² It was proved to be effective for the relief of symptoms of seasonal allergic rhinitis and was launched in the

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United States in August 1996.¹³⁻¹⁵ However, there was so far no clinical study of the perennial type of allergic rhinitis. Therefore, it was the objective of this study to assess the efficacy, safety and tolerability of this new antihistamine for the treatment of perennial allergic rhinitis in Thai patients.

MATERIALS AND METHODS

This was a multicenter, open-label, non-comparative study conducted in three otolaryngology centers in Bangkok, Thailand, i.e. Siriraj Hospital, Pramongkutklao Hospital and Chulalongkorn Hospital. The protocol of this study was approved by the Ethical Clearance Committee of each center and all subjects gave a written informed consent before study entry. Subjects were included if they were 16-65 years of age, having perennial allergic rhinitis symptoms for more than one year and had the total daily symptom scores (TSS) of ≥ 6 . The TSS derived from combining individual symptom scores for sneezing, rhinorrhea, nasal blockade, itchy nose/throat/palate and itchy/watery/red eyes which were recorded using a 5-point scale (0 = absent, to 4 = very severe). Patients were excluded if they were undergoing allergen immunotherapy, having vasomotor rhinitis or upper respiratory tract infection. Female patients who were pregnant or breast-feeding, patients with severe cardiac, hepatic, or renal disease, having a history of alcohol or drug abuse were also excluded. Certain previous medications had to be washed out for the period indicated in the protocol before enrolled in the study, i.e. other H₁ and H₂ antagonists ≥ 48 hours, astemizole ≥ 30 days, loratadine ≥ 7 days, nasal corticosteroids ≥ 14

days, oral corticosteroids ≥ 30 days, etc. The study medication was fexofenadine hydrochloride in 120 mg tablet form. The patients were instructed to record their allergy symptoms in the provided diary card every day before taking one tablet of the trial drug at 8.00 a.m. ± 1 hour for two weeks. Adverse events and concurrent medications were also recorded throughout the study. Concomitant medications were kept to a minimum during study period. For patients whose allergic symptoms were not adequately relieved by the study drug, topical or oral sympathomimetics were allowed and recorded as rescue medications. Patients were asked to bring their study medication to each clinic visit and compliance was checked by tablet count. In addition, the time until relief of symptoms commenced as perceived by the patient was also recorded together with presence of somnolence which was recorded on a visual analogue scale (VAS) in the diary card. ENT examination, vital signs and laboratory tests (i.e. fasting blood sugar, serum creatinine, urea, SGOT, SGPT, alkaline phosphatase, total bilirubin, total protein and albumin) including electrocardiograms (ECG) were performed at the first visit (V₁). Patients came back for follow up twice at day 7 \pm 2 (V₂) and day 14 \pm 2 (V₃) where ENT examination and vital signs were repeated. In one center (Siriraj Hospital) blood tests and ECG were also repeated at V₃. Assessment of the overall efficacy of the treatment was graded by patient and investigator separately using a five-point rating scale (1 = completely better, to 5 = worse) at V₂ and V₃. Efficacy of the treatment was evaluated from the daily symptom scores recorded by the patient, the findings from ENT examination at each visit

and from the global assessment of treatment by both the patient and the investigator. Safety and tolerability of the test drug were assessed from the incidence of treatment-related adverse events and the degree of somnolence. The changes of laboratory tests and ECG parameters from a baseline were also taken into consideration.

Statistical analysis

Demographic data were analyzed by descriptive statistics. Compared mean of TSS and of each symptom at V₁, V₂ and V₃ were analyzed by the paired-samples T test of 2-tailed with a 95% confidence interval of the difference. The time to onset of action was calculated as mean time to response \pm SEM. The number of patients experiencing adverse event were tabulated, graded for severity and imputation to the study drug. The presence of somnolence assessed in the diary card by VAS was analyzed by descriptive statistics.

RESULTS

Altogether 101 perennial allergic rhinitis patients were included in the study. Thirty-three were males and 68 were females. Their ages ranged from 16 to 56 years with mean age of 33.02 ± 9.33 . The average duration of their symptoms was 5.67 ± 5.66 years (ranging from 1-22 years). One patient did not follow up and 9 patients disqualified due to protocol violation resulting in 91 patients evaluable for efficacy analysis and 100 patients evaluable for safety analysis.

There was no change of pulse rate and blood pressure in any

subject at any visit. Blood chemistry which was tested before and after treatment in 22 patients (Siriraj Center) showed no statistical significant changes. ECG which was performed before and after treatment in 25 subjects also showed no abnormal findings. The average weekly symptom scores were significantly reduced from baseline for each symptom and also for total symptoms with and without nasal congestion (Table 1, Figs. 1 and 2). These changes were statistically significant when week 0 was compared to week 1 and week 2 but not when comparing week 1 and week 2. The onset of action of the test drug recorded by the patients ranged from 29 to 363 minutes with a mean onset of symptom relief of 2 hours and 12 minutes (132.4 ± 80.6 minutes, 95% CI = 110.0 ± 154.9). The overall effectiveness of the treatment assessed by the patients and the investigators were shown in Fig. 3. The percentage of combined "good", "very good", and "excellent" improvement was 67.3% in the patients' record and 70.4% in the record of the investigators. There was a statistically significant agreement between patients and investigators global assessment of

efficacy calculated by Kappa statistics.

During the two weeks of treatment, 19 patients reported 22 adverse events (AE) out of which 13 events were considered unrelated to the trial drug. Therefore, 9 AE were treatment-related and were reported from 8 patients (8%). Five events were classified as possible drug related, i.e. hand shaking, abdominal discomfort, drowsiness, weight gain and dry mouth which occurred in one patient each. Four events were probably drug related, i.e. chest discomfort, bitter taste and headache which happened in one patient each and increased appetite in two patients. All these AE were mild and tolerable; hence no patient had to be withdrawn from the study because of AE.

Concerning drowsiness, only one patient reported drowsiness as an AE. However, when all subjects were asked to evaluate the level of somnolence during the two-week treatment period, 98 patients responded as shown in Fig. 4.

DISCUSSION

In a comparative study to

characterize the dose-response relationship of fexofenadine HCl at dosages of 60, 120 and 240 mg twice a day for the treatment of 570 seasonal allergic rhinitis, Bernstein *et al.*¹⁴ concluded that fexofenadine HCl was both effective and safe for the treatment of ragweed seasonal allergic rhinitis. But no additional efficacy was found at higher dosages; therefore, 60 mg bid was recommended to be the optimal therapeutic dosage.¹⁵ Also in another study, there was no significant difference in efficacy between 120 mg OD and 180 mg OD doses in seasonal allergic rhinitis.¹⁶

In this trial, fexofenadine HCl 120 mg OD was proved to be effective and tolerable for the treatment of perennial allergic rhinitis. This once a day dosage is more convenient and should offer better compliance in clinical practice. The onset of action of fexofenadine HCl in this study is in accordance with the maximum plasma level following oral administration which is reached within one to three hours.^{10,17} Average time to onset of fexofenadine 60 mg and 120 mg was 60 minutes in ragweed allergy patients using controlled pollen

Table 1 Mean \pm SE of symptom scores and 95% confidence interval (CI) at week 0 (baseline), week 1 and week 2 after fexofenadine treatment

	Week 0		Week 1		Week 2	
	Mean \pm SE	95% CI	Mean \pm SE	95% CI	Mean \pm SE	95% CI
Blocked nose	2.15 \pm 0.09	1.97-2.33	1.32 \pm 0.10	1.12-1.53	1.20 \pm 0.11	0.98-1.41
Sneezing	2.16 \pm 0.09	1.98-2.34	0.87 \pm 0.09	0.69-1.05	0.75 \pm 0.09	0.57-0.93
Rhinorrhea	2.38 \pm 0.08	2.22-2.54	1.13 \pm 0.10	0.94-1.33	1.01 \pm 0.10	0.81-1.21
Itchy nose/palate and/or throat	2.07 \pm 0.10	1.86-2.28	0.97 \pm 0.11	0.75-1.18	0.82 \pm 0.09	0.63-1.00
Itchy/ watery/ red eyes	1.45 \pm 0.11	1.23-1.67	0.66 \pm 0.10	0.46-0.85	0.59 \pm 0.09	0.41-0.76
Total symptom scores (TSS)	10.20 \pm 0.28	9.63-10.77	4.88 \pm 0.33	4.22-5.53	4.36 \pm 0.35	3.67-5.04
TSS not including nasal congestion	8.06 \pm 0.26	7.55-8.57	3.62 \pm 0.28	3.06-4.19	3.16 \pm 0.27	2.62-3.70

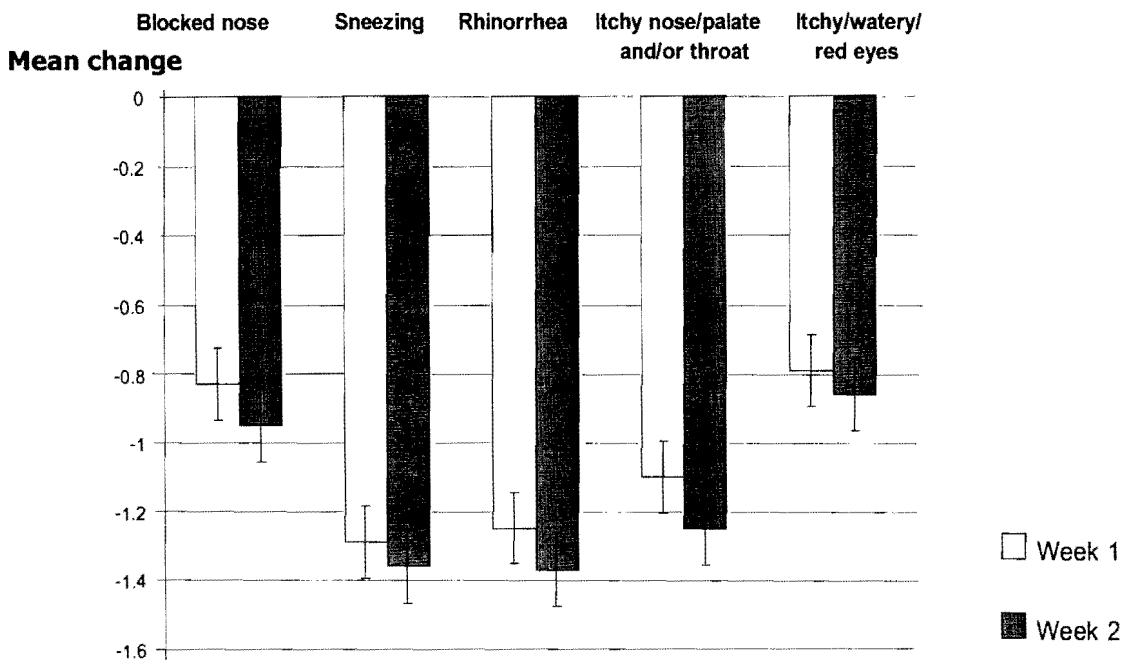


Fig. 1 Mean ± S.E. of reduction from a base line of each symptom at week 1 and week 2 after initiation of fexofenadine treatment ($p < 0.05$).

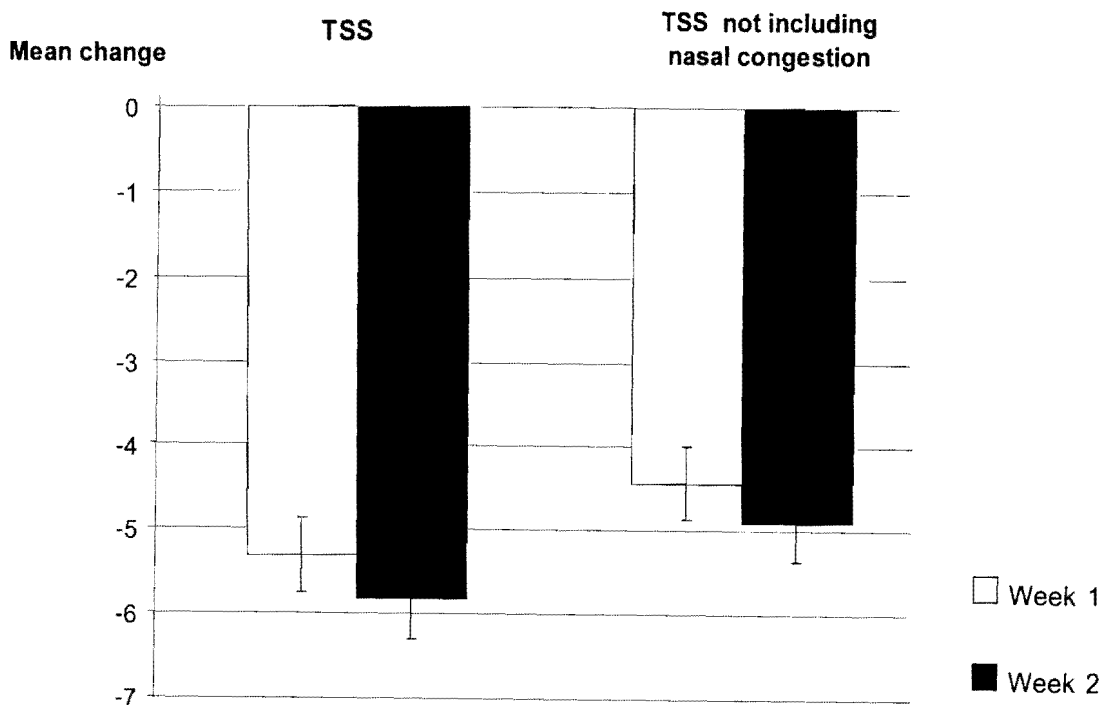


Fig. 2 Mean ± S.E. of reduction from a base line of the total symptom scores (TSS) and TSS without nasal congestion after week 1 and week 2 of fexofenadine treatment ($p \leq 0.05$).

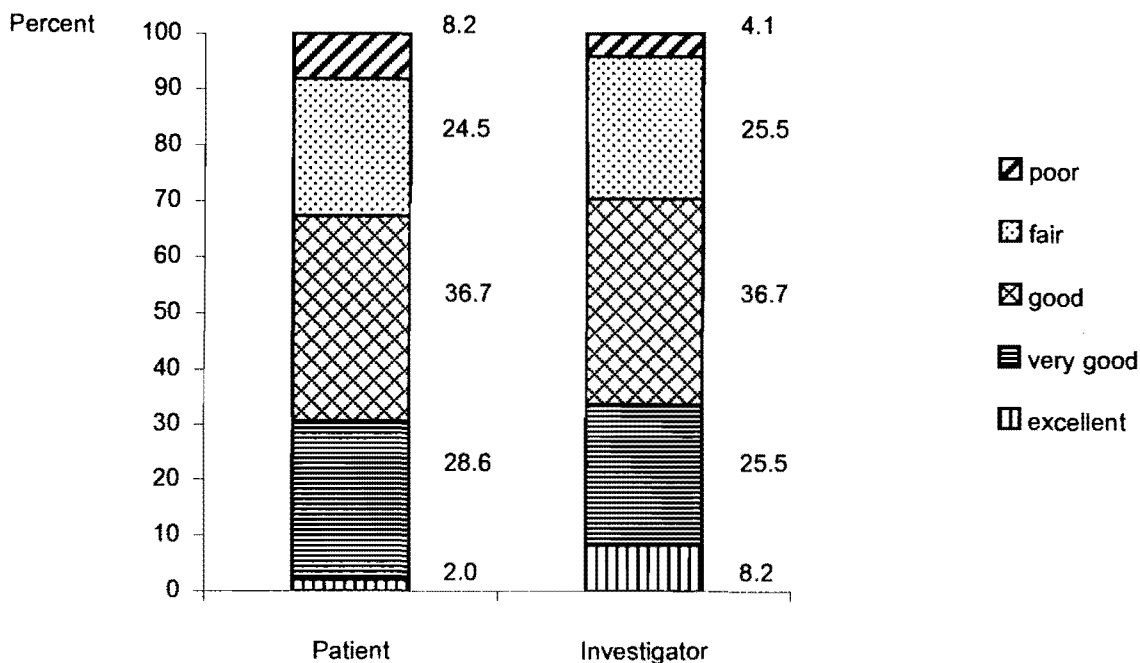


Fig. 3 Overall assessment of the efficacy of fexofenadine treatment by patients and investigators

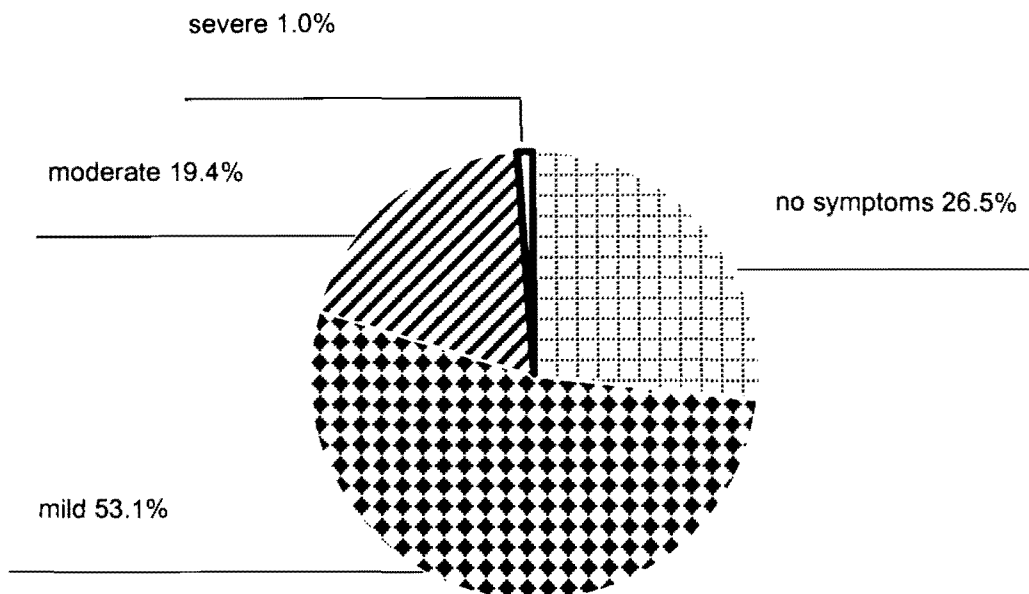


Fig. 4 Level of somnolence evaluated by 98 patients during the two weeks treatment with fexofenadine

exposure in an environmental exposure unit.¹⁸

Concerning the adverse events, in a meta-analysis of the placebo-controlled clinical trials involving 2,461 patients treated with fexofenadine HCl 20-240 mg bid, headache was the most frequently reported treatment-related adverse event.¹⁹ However, it occurred in similar frequency in the placebo treatment group. In this study, headache was only reported in one patient.

Fexofenadine was also proved to be truly non-sedative regardless of dose, i.e. fexofenadine at up to four times the recommended daily dose did not cause sedation and resulted in no impairment of cognitive and psychomotor performance.¹⁹⁻²¹ Fexofenadine did not impair driving performance and there was also no additive effect when taken together with alcohol.²² The sedative effect of fexofenadine 120 mg and 180 mg was studied in Thai healthy volunteers with similar results.^{23,24}

The impact of fexofenadine on quality of life was assessed in seasonal allergic rhinitis patients with 60 mg bid dose compared to placebo, the result clearly showed statistically significant improvements in disease-specific quality of life and performance impairment measures in the fexofenadine treated group.²⁵ Fexofenadine also showed some anti-allergic properties, e.g. inhibiting cytokine release and reducing of ICAM-1 expression when studied *in vitro*.^{26,27} However this effect has yet to be confirmed in a clinical study.

In conclusion, this study is the first trial of fexofenadine treatment in the perennial type of al-

lergic rhinitis. The results of this trial suggest that fexofenadine 120 mg OD is safe and effective in the treatment of perennial allergic rhinitis.

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