Multicenter Study of the Efficacy and Safety of Fexofenadine 60 mg Twice Daily in 108 Thai Patients with Chronic Idiopathic Urticaria

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Abstract

Fexofenadine is a non-sedating antihistamine indicated for relieving symptoms from allergic conditions with a rapid onset of action without cardiotoxic risks. Controlled studies showed that fexofenadine 180 mg daily provides significant relief of symptoms of chronic idiopathic urticaria (CIU). The purpose of this study was to demonstrate the efficacy and safety of fexofenadine 60 mg twice daily in Thai patients with CIU in a multicenter trial. Patients were assigned to receive twice daily doses of fexofenadine 60 mg for 6 weeks. Patients rated symptom severity every night, investigators rated patients' signs and symptoms at recruitment and at 1, 3 and 6 weeks. Ninety eight out of 108 patient (90.7%) completed the study. The patients reported 95 per cent improvement and, of those, 91 per cent had very favorable responses (excellent 15%, very good 42%, good 30%, fair 8%). The objective assessment by their physicians paralleled those responses. Fexofenadine provided a rapid clinical response that was significantly superior to before treatment in relieving symptoms of CIU ($p < 0.001$). Adverse events occurred in 20 cases (18.5%), mostly mild headache and drowsiness. Fexofenadine 60 mg twice daily provides effective relief of the symptoms of CIU with minimal adverse events.

Key word : Chronic Idiopathic Urticaria, Fexofenadine, Efficacy, Safety

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Fexofenadine is the most recently approved non-sedating antihistamine for treatment of seasonal allergic rhinitis, perennial allergic rhinitis (Canada) and chronic idiopathic urticaria (CIU)[1-4]. Fexofenadine is a highly specific H_1-receptor antagonist with a safety profile similar to placebo and is also well tolerated in subjects with renal or hepatic impairment, in children and in the elderly[5]. Fexofenadine is not associated with cardiotoxicity[6] and has been shown to have no significant effect on heart rate, PR interval, QRS width, QT interval or QTc.

A multicenter double-blind, randomized, placebo-controlled study in Europe (n = 222) using fexofenadine 60, 120, 180 and 240 mg, or placebo once daily for 6 weeks showed that fexofenadine 180 mg once daily was the optimal dose in the treatment of CIU[3]. However, another 4 weeks, multicenter double-blind, placebo-controlled study in the United States using fexofenadine 20, 60, 120 or 240 mg twice daily compared to placebo in 439 patients with moderate to severe pruritus and urticaria showed that doses of 60 mg twice daily or greater are equally effective[2]. This expands the options for the treating physician.

The purpose of this study was to add clinical data, by studying the efficacy and safety of fexofenadine 60 mg twice daily under conditions in Thailand in patients with CIU.

MATERIAL AND METHOD

A multicenter, open-labelled, non-comparative study of fexofenadine given orally twice daily in patients with CIU was carried out by dermatologists from 5 medical school hospitals in Thailand under "Good Clinical Practice (GCP)" control. The study protocol was approved by the ethic commitees of all hospitals. Eligible patients were patients who were at least 12 years old with symptoms of urticaria at least 3 times per week for not less than 6 consecutive weeks without apparent causes. A washout period from prior treatments were considered as follows: parenteral corticosteroids 90 days, oral corticosteroids 30 days, nedocromil or sodium cromoglycate 14 days, astemizole 30 days, loratidine 7 days, other H_1 and H_2 antagonists 48 hours.

Exclusion criteria were women who were not using adequate contraceptive measures or breast feeding or with pregnancy, patients with cardiac, renal, hepatic or rapidly progressing fatal diseases, patients with a history of alcohol consumption, drug abuse or hypersensitivity to fexofenadine or terfenadine, patients with mental conditions rendering them incapable of understanding the nature, scope and possible consequences of the study and/or evidence of an uncooperative attitude. Written informed consent was obtained from all study patients prior to entry into the study.

After a complete history and physical examination, laboratory assessments, and pregnancy testing which met the entry citeria, all patients were assigned to receive a twice daily dose of fexofenadine 60 mg for 6 weeks. The instruction to the study patients was to take the medication around 7 am and 7 pm each day for 6 consecutive weeks.

Symptom assessments by patients

Every patient was assigned to record the assessment of symptoms in a diary card every day at 7 pm. Patients rated the total number of wheals (0 = none, 1 = 1-5 wheals, 2 = 6-15 wheals, 3 = 16-25 wheals, 4 = >25 wheals), severity of itching (0 = none, 1 = mild; minor irritation; hardly noticeable; not annoying or troublesome, 2 = moderate; annoying and troublesome; may have interfered somewhat with normal daily activity and/or sleep, 3 = severe; very annoying and troublesome; substantially interfered with normal daily activity and/or sleep, 4 = very severe; warranted a visit to a physician), interference with sleep (0 = none, 1 = mild, 2 = moderate, 3 = severe), interference with normal daily activity (0 = none, 1 = mild, 2 = moderate, 3 = severe). Patients also rated levels of somnolence by using visual analogue scale (VAS). Overall effectiveness of treatment was recorded at the end of each visit (0 = poor; no relief/worse, 1 = fair; slight relief-symptoms are present and only minimal improvement, 2 = good; moderate relief-symptoms have noticeably improved but are still present and may be troublesome, 3 = very good; marked relief-symptoms have vastly improved and, although still present, are scarcely troublesome, 4 = excellent; complete relief-symptoms are not present). Every item of patient rating scales was explained and discussed with all patients before their diary cards were filled up.

Assessments by investigators

At baseline and at the end of week 1, 3, and 6 after treatment, all investigators rated patients' symptoms and signs by looking at the total number of wheals (0 = none, 1 = 1-5 wheals, 2 = 6-15 wheals, 3 = 16-25 wheals, 4 = >25 wheals), longest diameter of wheals on average (0 = absent, 1 = <0.5 cm, 2 = 0.5-2.0 cm, 3 = >2.0-4.0 cm, 4 = >4.0 cm), intensity of erythema on average (0 = absent, 1 = slight/pale, 2 = definite/red, 3 = extreme/bright red), extent of skin involved (0 = none, 1 = 1-10% of body, 2 = 11-30%, 3 = 31-50%, 4 = >50%), severity of pruritus (0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe). At final visit, all investigators evaluated the overall efficacy of treatment by using the following rating scales on results as : 0 = poor, 1= fair, 2 = good, 3 = very good and 4 = excellent.

Statistical analysis

All analyses were performed under 95 per cent confidence level by using program SPSS version 9.01 for Windows. Demographic data of all patients, patients who completed or withdrew from the study were analysed by using descriptive methods and will be reported in the result part. Differences in ages, proportion of sex, mean body weight, mean duration of CIU, average day with wheals between data from patients who completed and from those who withdrew from the study were compared using *t*-test for continuous data and chi-square test for categorical data. For efficacy analyses, scores from the assessment by patients at pretreatment and at the end of week 1 and week 6 were compared using the paired *t*-test. Moreover, scores from patients were compared between at pretreatment and at day 1 and 2 after treatment. The assessment by doctors was also performed in the same period.

Safety analysis

At each of the three visits (the end of week 1, 3, and 6) all patients or observed adverse events were recorded.

RESULTS

Demography

Of 108 patients who entered into the study, 10 patients (9.3%) withdrew from the study (7 were lost to follow-up, 1 was due to lack of efficacy, 1 was due to protocol violation, 1 was due to adverse event). There were no significant differences in ages, proportion of sex, mean body weight, mean duration of CIU and average days with wheals between data from patients who completed and from those who withdrew from the study. Of the 98 patients who completed the study, 76 were female, 22 were male, with mean age of 35.7 (SEM 1.3) years (the youngest was 14 and the oldest was 87 years old), mean body weight was 56.0 (SEM 1.0) kgs. Mean duration of urticaria was 98.3 (SEM 18.6) weeks (range 6-1040 weeks). Average day with wheals was 6.0 (SEM 0.2) days per week.

Table 1. Patients assessment of CIU by time of follow-up.

Outcome	D0* (n=104)	D1** (n=104)	D2** (n=103)	D0:D1*** (df=103)	D0:D2*** (df=102)
No of wheals[1]	2.56	1.80	1.50	0.76, p<0.001	1.04, p<0.001
Itching[2]	2.27	1.39	1.18	0.88, p<0.001	1.08, p<0.001
Interfered with sleep[3]	1.53	0.99	0.78	0.54, p<0.001	0.75, p<0.001
Interfered with normal daily activity[4]	1.66	1.15	0.98	0.50, p<0.001	0.66, p<0.001

D0* : Day 0 or first assessment

D1**, D2**: 1 day and 2 days after treatment

D0:D1***, D0:D2***: paired *t*-test between day 0 to 1 day after treatment, day 0 to 2 days after treatment

No of wheals[1]: numbers of wheals (mean): 0=none; 1=1-5 wheals; 2 = 6-15 wheals; 3 = 16-25 wheals; 4 = more than 25 wheals

Itching[2]: rating of itching (mean): 0 = none; 1 = mild (minor irritation); 2 = moderate (annoying and troublesome); 3 = severe (very annoying and troublesome); 4 = very severe (warranted a visit to doctor)

Interfered with sleep[3] (mean): 0 = none; 1 = mild; 2 = moderate; 3 = severe

Interfered with normal daily activity[4] (mean): 0 = none; 1 = mild; 2 = moderate; 3 = severe

Table 2. Patients assessment of CIU by time of follow-up.

Outcome	D0*	W1**	W3**	W6**	D0:W1***	D0:W6***
No of wheals[1]	2.50	1.25	1.12	0.98	1.26, p<0.001	1.52, p<0.001
Itching[2]	2.12	1.06	0.95	0.80	1.06, p<0.001	1.33, p<0.001
Interfered with sleep[3]	1.33	0.60	0.52	0.48	0.72, p<0.001	0.85, p<0.001
Interfered with normal daily activity[4]	1.37	0.73	0.71	0.62	0.63, p<0.001	0.74, p<0.001

D0*: Day 0 or first assessment
W1**, W3**, W6**: Week 1 visit, Week 3 visit, Week 6 visit/final visit
D0:W1***, D0:W6***: paired *t*-test between day 0 to week 1 visit, day 0 to week 6 visit/final visit
No of wheals[1]: numbers of wheals (mean): 0 = none; 1 = 1-5 wheals; 2 = 6-15 wheals; 3 = 16-25 wheals; 4 = more than 25 wheals
Itching[2]: rating of itching (mean): 0 = none; 1 = mild (minor irritation); 2 = moderate (annoying and troublesome); 3 = severe (very annoying andtroublesome); 4 = very severe (warranted a visit to doctor)
Interfered with sleep[3] (mean): 0 = none; 1 = mild; 2 = moderate; 3 = severe
Interfered with normal daily activity[4] (mean): 0 = none; 1 = mild; 2 = moderate; 3 = severe

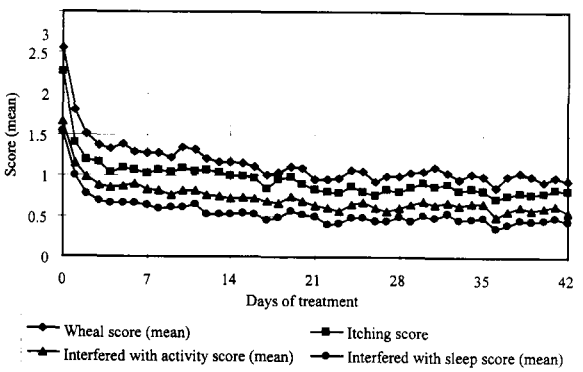

Fig. 1. Patient assessment of CIU by days of treatment.

Efficacy

Patients' assessment

Analyses of patients'daily ratings showed that fexofenadine significantly (p<0.001) reduced all symptoms of urticaria within 24 hours of the first dose (Table 1). The scores of number of wheals, degree of itching decreased from 2.56, and 2.27 at baseline to 1.80 and 1.39 respectively at day 1 (p<0.001). At the end of treatment week 1 and week 6, fexofenadine had significantly (p< 0.001) reduced the number of wheals, severity of itching, interference with sleep and with normal daily activity compared with before treatment (Table 2, Fig. 1).

At the end of treatment, patients rated overall effectiveness of treatment as follows: excellent 15.3 per cent, very good 41.8 per cent, good 29.6 per cent, fair 8.2 per cent, and poor 5.1 per cent.

Investigators' assessment

At the end of treatment week 1 and week 6, fexofenadine had significantly (p<0.001) reduced the number of wheals, average diameter of wheals, intensity of erythema, and severity of pruritus compared with before treatment (Table 3, Fig. 2). Final assessment of overall effectiveness of the treatment by investigators was as follows: excellent 15.3 per cent, very good 31.6 per cent, good 35.7 per cent, fair 13.3 per cent, and poor 4.1 per cent.

Adverse events

Adverse events occurred in 20 patients (18.5% of 108 cases), or 23 events. One patient withdrew from the study even though her headache was mild. From 23 events, each of 18 patients experienced one adverse event, 1 patient had 2 adverse events, and 1 patient had 3 adverse events. The common adverse events were headache and drowsiness (8 events each; 7.4%), the others were dizziness (3 events), increased appetite (2 events), increased weight, and cough (1 event each). The degree of treatment–related adverse events were mainly graded as mild.

Drowsy visual analogue scale (VAS) analysis showed a slight increase of VAS in the first few weeks of treatment (Fig. 3).

DISCUSSION

Fexofenadine is a new non-sedating, long acting, highly selective peripheral H_1-

Table 3. Doctor assessment of skin condition by time of follow-up.

Outcome	D0*	W1**	W3**	W6**	D0:W1***	D0:W6***
No of wheals[1]	1.33	0.63	0.56	0.52	0.72, p<0.001	0.81, p<0.001
Diameter[2]	1.29	0.60	0.53	0.42	0.69, p<0.001	0.87, p<0.001
Erythema[3]	1.03	0.44	0.47	0.38	0.60, p<0.001	0.65, p<0.001
Extent of skin area[4]	0.96	0.45	0.40	0.37	0.52, p<0.001	0.59, p<0.001
Pruritus[5]	1.09	0.42	0.46	0.29	0.69, p<0.001	0.81, p<0.001

D0*: Day 0 or first assessment
W1**, W3**, W6**: Week 1 visit, Week 3 visit, Week 6 visit/final visit
D0:W1***, D0:W6***: paired *t*-test between day 0 to week 1 visit, day 0 to week 6 visit/final visit
No of wheals[1]: numbers of wheals (mean): 0=none; 1=1-5 wheals; 2 = 6-15 wheals; 3 = 16-25 wheals; 4 = more than 25 wheals
Diameter[2]: longest diameter of wheals on average (mean): 0 = absent; 1 = less than 0.5 cm; 2 = 0.5 to 2.0 cm; 3 = > 2.0–4.0 cm; 4 = more than 4.0 cm
Erythema[3]: intensity of erythema on average (mean): 0 = absent; 1 = slight/pale; 2 = definite/red; 3 = extreme/bright red
Extent of skin area[4]: extent of skin involved (mean): 0 = none; 1 = small (1-10%); 2 = moderate (11-30%);3 = severe (31-50%); 4 = very severe (>50%)
Pruritus[5]: rating of pruritus (mean): 0=none; 1=mild (minor irritation); 2=moderate (annoying and troublesome); 3=severe (very annoying and troublesome); 4 = very severe (warranted a visit to doctor)

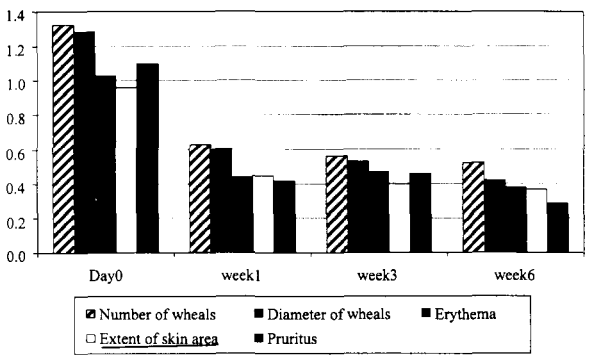

Fig. 2. Doctor assessment of skin condition.

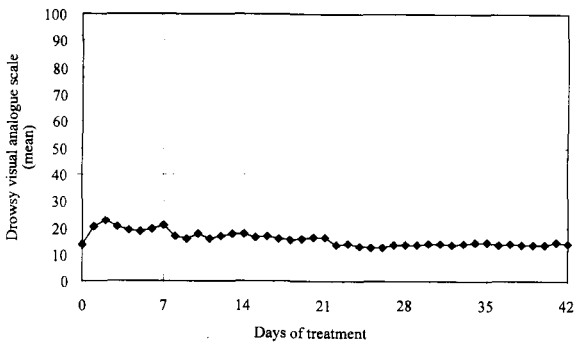

Fig. 3. Visual analogue scale of drowsiness by days of treatment.

receptor antagonist. In isolated guinea-pig ileum, fexofenadine was more selective than terfenadine in antagonizing histamine-induced contractions without interfering with those induced by acetylcholine and calcium chloride(2). The results suggest that fexofenadine has no anticholinergic activity and no calcium channel blocking effect. Fexofenadine is active without prior metabolism. It undergoes negligible hepatic metabolism and has no effect on cytochrome P-450, CYP 3A4(7).

Fexofenadine has been investigated extensively for possible electrophysiological effects. The lack of an effect on K^+ channels is consistent with the ECG evaluation indicating no effect on repolarization. Clinical evidence from dose-tolerance, long-term safety, drug interaction and controlled efficacy trials has demonstrated that fexofenadine does not prolong QT_C. Concomitant administration of fexofenadine with either erythromycin or ketoconazole has no effect on QT_C(6). No case of fexofenadine-associated torsades de pointes has been observed in controlled trials in more than 6000 patients.

Although the pathogenesis of CIU is not fully understood, many cases have been associated with IgG autoantibodies against IgE or the IgE

receptor ($F_{C\varepsilon}R$ I) which can activate mast cells [8,9]. As a consequence, antihistamines are the mainstay treatment of patients with CIU.

The results of this study demonstrated that fexofenadine 60 mg twice daily resulted in very effective relief of symptoms of CIU in Thai patients. The clinical benefits occurred rapidly and within the first day. A previous study done in Europe by Pual et al[3] showed that fexofenadine 120 mg once daily produced a statistically significant improvement in pruritus score in patients with CIU compared with placebo. However, the statistically significant improvement in total symptom scores between the treatment groups and placebo was seen in the 180 mg and 240 mg groups, not in 60 mg and 120 mg groups. Another study group done in the U.S.A. using fexofenadine 20, 60, 120 and 240 mg twice daily compared to placebo showed that the dose of 60 mg twice daily or greater was most effective[2]. Eventhough fexofenadine has a serum half-life of 14.4 hours[4]. The study result from the U.S.A. and our study suggest that a split dose regimen is equally effective when compared to single total dose.

The common adverse events were mild headache and drowsiness (7.4% each). Even though our study was an open study, in the previous placebo controlled once-daily dosing study, adverse events considered to be treatment-related were reported in 24.5 per cent of 171 patients receiving fexofenadine, and 33 per cent of 51 patients receiving placebo. The most frequently reported treatment related adverse event was headache which was reported by 12 per cent of patients receiving fexofenadine and 14 per cent of those receiving placebo. Two patients in the placebo group reported drowsiness, whereas, no fexofenadine-treated patients reported drowsiness. The frequency of treatment-related adverse events was not statistically different between the fexofenadine and placebo group[2]. The severity of the adverse events was mainly graded as mild or moderate.

The degree of drowsy VAS in our study demonstrated a slight increase in VAS in the first few weeks and returned to baseline level in spite of continuing the medication. No peripheral anticholinergic effects such as blurred vision, dry mouth, urinary retention, and constipation were detected.

In summary, this study demonstrates that fexofenadine is an effective antihistamine in the treatment of CIU. Fexofenadine 60 mg twice daily provided effective relief of symptoms of CIU with minimal adverse events in a Thai population.

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การศึกษาประสิทธิภาพและผลข้างเคียงของการใช้ยาเฟกโซฟีนาดีนขนาด 60 มิลลิกรัม วันละ 2 ครั้ง ในผู้ป่วยโรคลมพิษเรื้อรัง

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เฟกโซฟีนาดีน เป็นยาต้านฮีสตามีนตัวใหม่ที่ออกฤทธิ์ยาว และไม่ทำให้ง่วง ยานี้ใช้รักษาโรคภูมิแพ้โดยออกฤทธิ์เร็วและไม่มีอันตรายต่อหัวใจ การศึกษาที่ทำในต่างประเทศ พบว่า ยานี้ในขนาด 180 มิลลิกรัมต่อวัน ได้ผลดีในการรักษาโรคลมพิษเรื้อรัง คณะผู้วิจัยได้ทำการศึกษาประสิทธิภาพและผลข้างเคียงของการใช้ยาเฟกโซฟีนาดีนขนาด 60 มิลลิกรัม วันละ 2 ครั้งในผู้ป่วยคนไทยที่เป็นโรคลมพิษเรื้อรังเป็นเวลา 6 สัปดาห์ โดยเป็นการศึกษาร่วมของ 5 สถาบัน ผู้ป่วยประเมินอาการของโรคลมพิษทุกคืนและแพทย์ประเมินผลการรักษาก่อนและหลังได้ยา 1, 3 และ 6 สัปดาห์ ผู้ป่วย 98 ใน 108 ราย (90.7%) ได้รับยาครบจนกระทั่งประเมินผล 95% ของผู้ป่วยประเมินอาการว่าดีขึ้นเมื่อได้รับยาเทียบกับก่อนการรักษา โดย 91% ได้ผลตั้งแต่ดีปานกลางขึ้นไป (ดีเลิศ 15%, ดีมาก 42%, ดี 30%, ปานกลาง 8%) การประเมินผลการรักษาโดยแพทย์ให้ผลคล้ายคลึงกัน ยาลดอาการลมพิษภายใน 1 วัน อาการข้างเคียงของยาพบในผู้ป่วย 20 ราย (18.5%) ที่พบบ่อยได้แก่อาการปวดศีรษะและง่วงซึม (อย่างละ 8 ราย) โดยสรุป ยาเฟกโซนาดีนในขนาด 60 มิลลิกรัม วันละ 2 ครั้ง ได้ผลดีในการรักษาโรคลมพิษเรื้อรังในคนไทย โดยมีฤทธิ์ข้างเคียงน้อย

คำสำคัญ : โรคลมพิษเรื้อรัง, ประสิทธิภาพของยาเฟกโซฟีนาดีน

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