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Comparative study between the efficacy of local-made and original fexofenadine in persistent allergic rhinitis

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Problem/background : *Fexofenadine is known as a non-sedative antihistamine effective for persistent allergic rhinitis. Physicians usually prescribe local-made or original fexofenadine according to their preferences without any clinical trials to support their decisions. Our question is whether a local-made fexofenadine is as clinically effective as an original one for the treatment of persistent allergic rhinitis.*

Objective : *To compare between the efficacy of a local-made and an original fexofenadine in the treatment of persistent allergic rhinitis*

Design : *Double-blind, crossover clinical trial*

Setting : *OPD Clinic, King Chulalongkorn Memorial Hospital*

Material and Methods : *Cases of persistent allergic rhinitis positive to Dermatophagoides Pteronyssinus were recruited. Patients were assigned to receive one-week course of either types of fexofenadine (Fenafex: a local-made or Telfast: an original). After a wash-out period, they received another course of the other type of drug. Daily symptom score and any adverse effects were recorded. Intradermal test, peak nasal inspiratory flow, symptoms and quality of life score were measured before and after the treatments. The efficacies of the two drugs were then compared.*

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- Results** : *A local-made fexofenadine is not significantly different from an original one (imported) when used to suppress allergen-induced wheal and flare reaction, or to increase peak nasal inspiratory flow, or to decrease clinical symptoms and to improve the quality of life of the patient. Also, adverse effects of both drugs are not different.*
- Conclusions** : *The efficacy of a local-made fexofenadine is similar to the original.*
- Keywords** : *Persistent allergic rhinitis, Fexofenadine.*

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กรเกียรติ์ สนิทวงศ์, สุพินดา แสงพานิชย์, ทรงกลด เอี่ยมจตุรภัทร, จันทิมา พรรณาโส.
เปรียบเทียบประสิทธิผลของยา fexofenadine ที่ผลิตในประเทศกับยาดันแบบในผู้ป่วย
persistent allergic rhinitis. จุฬาลงกรณ์เวชสาร 2550 พ.ศ. - มี.ย; 51(5): 289 - 302

เหตุผลของการทำวิจัย : Fexofenadine เป็นยาดันฮิสตามีนรุ่นใหม่ที่ควบคุมอาการของโรค
persistent allergic rhinitis ได้ดี ปัจจุบันยังไม่มีการศึกษาเปรียบเทียบ
ประสิทธิผลของยาที่ผลิตในประเทศกับยาดันแบบมาก่อน คำถาม
การวิจัยคือ fexofenadine ที่ผลิตในประเทศให้ผลการรักษาต่อ
persistent allergic rhinitis ได้เท่าเทียมกับยาดันแบบหรือไม่

วัตถุประสงค์ : เพื่อเปรียบเทียบประสิทธิผลของยา fexofenadine ที่ผลิตจากผู้ผลิตใน
ประเทศ กับยาดันแบบในการรักษาผู้ป่วย persistent allergic rhinitis

รูปแบบการวิจัย : การศึกษาทางคลินิกแบบทดลอง

สถานที่ทำการศึกษา : คลินิกผู้ป่วยนอก โรงพยาบาลจุฬาลงกรณ์

ตัวอย่างและวิธีการศึกษา : ผู้ป่วย persistent allergic rhinitis ที่ให้ผลบวกต่อ Dermatophagoides
Pteronyssinus จะได้รับ fexofenadine เป็นเวลา 7 วัน ซึ่งอาจเป็นยา
ในประเทศ (Fenafex) หรือยาดันแบบและจะต้องบันทึกอาการประจำ
วันและอาการไม่พึงประสงค์จากการใช้ยาด้วย หลังจากหยุดพักการใช้
ยา 2 สัปดาห์ผู้ป่วยจะได้รับยาชนิดที่ 2 ข้อมูลที่จะนำมาวิเคราะห์
ได้แก่ allergen-induced intradermal test ปริมาณลมหายใจเข้า
อาการภูมิแพ้ ปัญหาคุณภาพชีวิต

ผลการศึกษา : ยา fexofenadine ที่ผลิตในประเทศไม่มีความแตกต่างทางสถิติจากยา
ดันแบบในการลดปฏิกิริยาภูมิแพ้ทางผิวหนัง เพิ่มปริมาณลมหายใจ
เข้า ลดอาการภูมิแพ้ เพิ่มคุณภาพชีวิต และอาการไม่พึงประสงค์จาก
การใช้ยา

สรุป : ยา fexofenadine ที่ผลิตในประเทศมีประสิทธิผลทางคลินิกไม่ต่างจาก
ยาดันแบบ

คำสำคัญ : โรคภูมิแพ้จมูกอักเสบเรื้อรัง, fexofenadine

Persistent allergic rhinitis is a common chronic nasal disease in Thailand. Its symptoms include itchy nose, sneezing, rhinorrhea and nasal obstruction. The associated symptoms are itchy palate, throat, and/or ear, cough, phlegm and itchy watery eyes. These may cause a negative impact on the quality of life and daily activities of the patient. As a result, working days and school days are probably continually interrupted. Moreover, without proper treatment, persistent allergic rhinitis can exacerbate asthma, rhinosinusitis, conjunctivitis and other respiratory infections.

Fexofenadine has been a well-known, non-sedating antihistamine indicated for relieving symptoms from allergic rhinitis since 2004. Its chemical formula is terfenadine carboxylate hydrochloride. Being an active metabolite of terfenadine, fexofenadine has no cardiac risks since hepatic metabolism is negligible.⁽¹⁾ Besides, it has been proved to be not distributed to the central nervous system (CNS) and having high selectivity for peripheral histamine H₁-receptors. Having no muscarinic effect, it does not cause dry mouth. After administration of fexofenadine, median time of having significant clinical improvement is 60 minutes.⁽²⁾ It is safe for both adults and children as there was no significant difference in adverse events in children, aged 6-11 years, between fexofenadine and placebo.⁽³⁾ Not only for allergic rhinitis, it is also efficacious for patients suffering with chronic idiopathic urticaria.⁽⁴⁾

In Thailand, physicians may prescribe a local-made or an original fexofenadine up to their preferences without any clinical trials to support their decisions. Our question is whether a local-made fexofenadine is as clinically effective as an original

one for persistent allergic rhinitis. The objective of this study is to compare between the efficacy of a local-made and an original fexofenadine (imported) in the treatment of persistent allergic rhinitis.

Population

Patients, presenting with persistent allergic rhinitis at the Out patient Clinic, King Chulalongkorn Memorial Hospital from October 2006 to March 2007, were recruited. The diagnostic criteria of persistent allergic rhinitis followed the classification of the working group on allergic rhinitis and its impact on asthma (ARIA) 2001. The age was 18 to 60. All patients were requested to sign their informed consents before their participation in the study. They should be healthy without any chronic underlying diseases, and their skin prick tests were positive to *Dermatophagoides Pteronyssinus*. The exclusion criteria included active rhinosinusitis, dermatographism, having immunotherapy during the past two years, pregnancy, lactation and β blocker user. All participants had been clearly explained about the objectives, methods of the study and also probable adverse effects of fexofenadine.

Methods

The Chulalongkorn Institution Review Board and the Ethics Committee, Faculty of Medicine, Chulalongkorn University approved the study protocol. All subjects were asked to stop using antihistamine, oral decongestant, antileukotriene, topical corticosteroid for two weeks and oral corticosteroid for four weeks. The main outcome of this study was allergen-induced wheal and flare, measured by intradermal injection with 0.2ml of 1:2500

Dermatophagoides Pteronyssinus. Secondary outcomes were peak nasal inspiratory flow, the quality-of-life score, daily symptom score and adverse drug reactions. Peak nasal inspiratory flow (PNIF) was measured by using In-Check Nasal, manufactured by Clement Clarke International, UK. Current symptoms and trouble of daily life were scored from 0 to 4, using The Quality of Life Questionnaire of Allergic Rhinoconjunctivitis (Rcq-36), created by Chaweewan Boonnag. The copyright of this questionnaire belongs to Mahidol University and the authors were allowed by the owner to use it. Score 0 means having no symptoms or no trouble and score 4 means experiencing the highest degree of symptom/trouble severity. Otolaryngologic symptoms in the questionnaire included rhinorrhea, itchy nose, nasal obstruction, sneezing, cough, dry mouth and phlegm. Other symptoms included itchy eyes, irritated eyes, tear, eye discomfort, dull head, fatigue, weakness, body ache, headache, sleepiness. Also, work/study difficulty, exercise disability, sleep disturbance, social disturbance, emotional disturbance, perception of general health trouble and work/study time missed per month were asked in the questionnaire.

Medicine given to subjects was randomized by coin tossing. The local made fexofenadine, used in the present study was Fenafex, manufactured by Sriprasit Pharma, Thailand, Reg No. 1A 23/47(NG), Batch No. 5TG139, bought from the Silom branch of Fascino drug store. The original fexofenadine was Telfast, Reg No. 1C11/43(N), Batch No.291D023, manufactured by Aventis pharmaceuticals Inc., USA, bought from the same drug store on the same day.

The subjects were requested to score their otolaryngologic symptoms twice daily from the first day up to one week. After seven days, allergen-induced wheal and flare, PNIF, trouble of life score were measured again. The wash-out period was two weeks. During this period, patients needed to stop using antihistamine, decongestant, antileukotriene, and corticosteroid. Then patients would receive the other kind of fexofenadine for seven days. Daily symptom score, allergen-induced wheal and flare, PNIF, trouble of life score were recorded again.

All data of the pre-treatment and post-treatment with the local-made and original fexofenadine were compared by using Repeated Annova. A comprehensive statistics software SPSS 13 was used to analyze all data.

Table 1. Mean diameter (mm) of wheal and flare of pre-treatment and post-treatment with local-made and original drugs. P value indicated significance for local-made and original drugs comparison.

	Pretreatment	local	original	Local vs original		Local vs pretreatment		Original vs pretreatment	
				95 % CI	P value	95 % CI	P value	95 % CI	P value
Wheal (mm)	11.13	9.00	9.59	-2.16 - 0.97	1	0.07 - 4.19	0.04 *	-0.18 - 3.26	0.09
Flare (mm)	32.48	23.81	23.97	-4.54 - 4.21	1	4.36 - 12.98	<0.001 *	4.32 - 12.69	<0.001*

* statistic significance

Table 2. Mean data of other outcomes of pre-treatment and post-treatment with local-made and original drugs. P value indicated significance for local-made and original drugs comparison.

	Pretreatment	local	original	Local vs original		Local vs pretreatment		Original vs pretreatment	
				95 % CI	P value	95 % CI	P value	95 % CI	P value
PNIF (L/min)	73.73	74.63	74.45	-10.54 – 10.90	1	10.30 – 8.51	1	-10.48 – 9.05	1
Otolaryngologic symptoms	1.64	1.07	0.98	-0.13 – 2.99	0.42	0.32 – 0.82	<0.001*	0.45 – 0.86	<0.001*
Other symptoms	1.40	0.92	0.78	-0.11 – 0.38	0.56	0.18 – 0.76	0.001*	0.35 – 0.87	<0.001*
Work / study	0.90	0.52	0.43	-0.18 – 0.36	1	0.02 – 0.75	0.03*	0.13 – 0.81	0.003*
Exercise disability	0.90	0.67	0.53	-0.15 – 0.42	0.74	-0.19 – 0.66	0.52	-0.01 – 0.75	0.06
Slept disturbance	1.51	0.95	0.86	-0.18 – 0.36	1	0.20 – 0.91	0.001*	0.26 – 1.03	<0.001*
Social disturbance	1.03	0.70	0.68	-0.26 – 0.31	1	-0.05 – 0.70	0.11	0.00 – 0.69	0.04*
Emotional disturbance	2.01	1.08	0.98	-0.28 – 0.48	1	0.52 – 1.33	<0.001*	0.62 – 1.44	<0.001*
General health trouble perception	2.16	1.75	1.83	-0.47 – 0.31	1	0.12 – 0.68	0.003*	0.01 – 0.63	0.037*
Work /study time missed (day per month)	0.64	0.45	0.56	-0.41 – 0.19	1	-0.14 – 0.52	0.49	-0.23 – 0.39	1

* statistic significance

Table 3. Mean daily symptom score after treatment.

Otolaryngologic symptoms	Fenafex	Telfast	P value
Day1	1.01	0.78	0.01 *
Day2	0.95	0.71	0.02 *
Day3	0.83	0.67	0.11
Day4	0.72	0.72	0.99
Day5	0.71	0.74	0.82
Day6	0.72	0.65	0.44
Day7	0.67	0.68	0.93

* statistic significance

Table 4. Mean adverse effect score after treatment.

Adverse effects	Fenafex	Telfast	P value
sleepy	0.64	0.54	0.35
dizzy	0.21	0.13	0.37
nausea	0.02	0.08	0.32
fatigue	0.54	0.48	0.66
dyspepsia	0.23	0.40	0.11
rash	0.10	0.08	0.66

Results

There were 200 cases of persistent allergic rhinitis presented to our clinic during October 2006 to March 2007. Ninety-nine were positive to *Dermatophagoides Pteronyssinus* by skin prick test. Forty-five decided not to participate with the study due to personal reasons. Seventeen of fifty-four did not complete the protocol. This was because of patient loss (10 cases), rhinosinusitis (3 cases) and allergy to fexofenadine (4 cases).

Of the thirty-seven cases who completed the study, there were 19 males (51.35 %) and 18 females (48.65 %). Their age ranged from 18 to 60. The mean age was 35.83. Eighteen received the local-made fexofenadine before crossing over to the original one.

The local-made and original fexofenadines were not statistically different for the effect on allergen-induced wheal suppression (95 % CI= -2.16 – 0.97, $p = 1$) and flare suppression (95 % CI= -4.54 – 4.21, $p = 1$). Also, both drugs could increase the peak nasal inspiratory flow, not differently from each other (95 % CI= -10.54 – 10.90, $p = 1.0$).

After one-week treatment, otolaryngologic and other symptoms were reduced indifferently by both medicines (95 % CI= -0.13 – 0.29, $p = 0.42$ and 95 % CI= -0.11 – 0.38, $p = 0.56$ respectively). They were not different from each other in the improvement

of the work and study performance (95 % CI= -0.18 – 0.36, $p = 1.0$), the ability of exercise (95 % CI= -0.15 – 0.42, $p = 0.74$), the sleep (95 % CI= -0.18 – 0.36, $p = 1.0$), the social performance (95 % CI= -0.26 – 0.31, $p = 1$), the emotion (95 % CI= -0.28 – 0.48, $p = 1.0$) and the general health perception (95 % CI= -0.47 – 0.31, $p = 1.0$).

Before treatment, the mean of work/study time missed was 0.64 day per month and it was 0.45 and 0.56 day per month after administration of the local-made and original fexofenadines respectively. Also, this was not significantly different (95 % CI= -0.41 – 0.19, $p = 1.0$)

Otolaryngologic symptoms decreased with both treatments from the first until the seventh day. By comparing day for day, the original fexofenadine could reduce otolaryngologic symptoms significantly more than the local-made one during the first two days (day 1, $p = 0.01$ and day 2, $p = 0.02$). After that, both treatments caused the same results.

There were adverse effects in some subjects including sleepiness, dizziness, nausea, fatigue, dyspepsia and skin rash from both drugs. The severity of all effects was mild as all mean scores were less than 1. There was no difference between the adverse effects of the two drugs. The mean score of adverse effects was shown in the table.

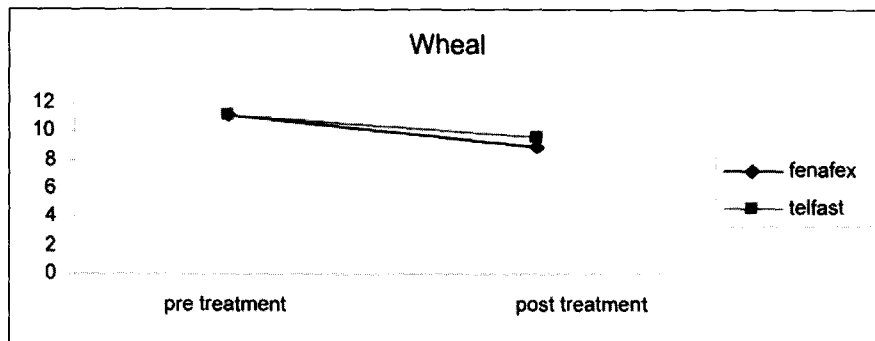


Figure 1. Pre-treatment and post-treatment wheal of local-made and original fexofenadine.

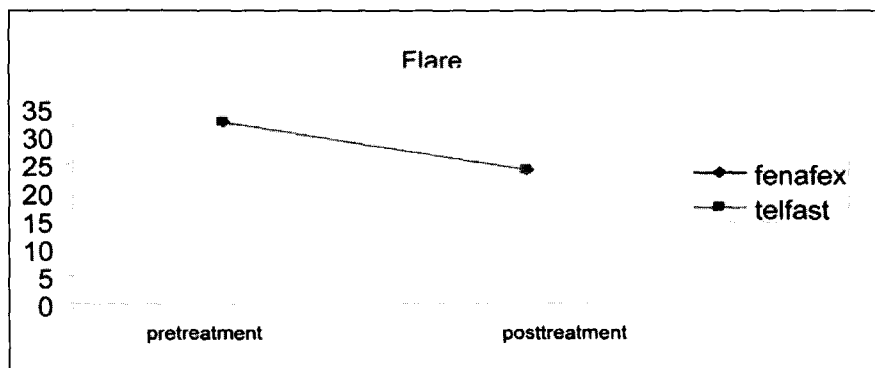


Figure 2. Pre-treatment and post-treatment flare of local-made and original fexofenadine.

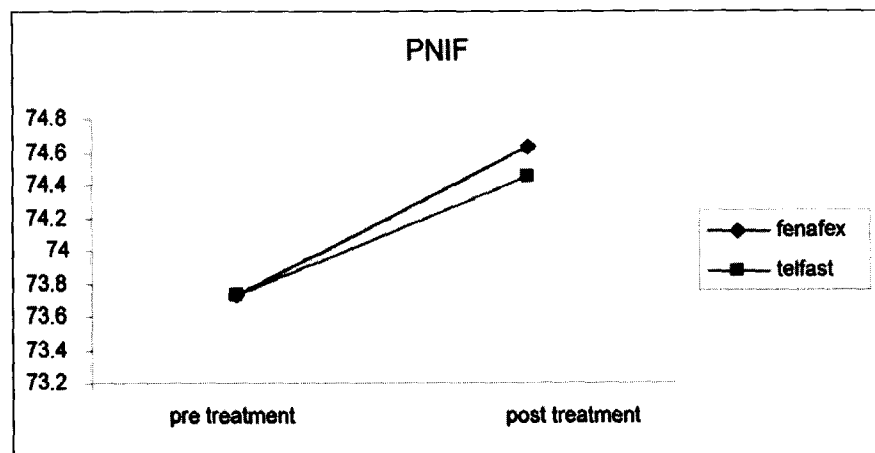


Figure 3. Pre-treatment and post-treatment PNIF of local-made and original fexofenadine.

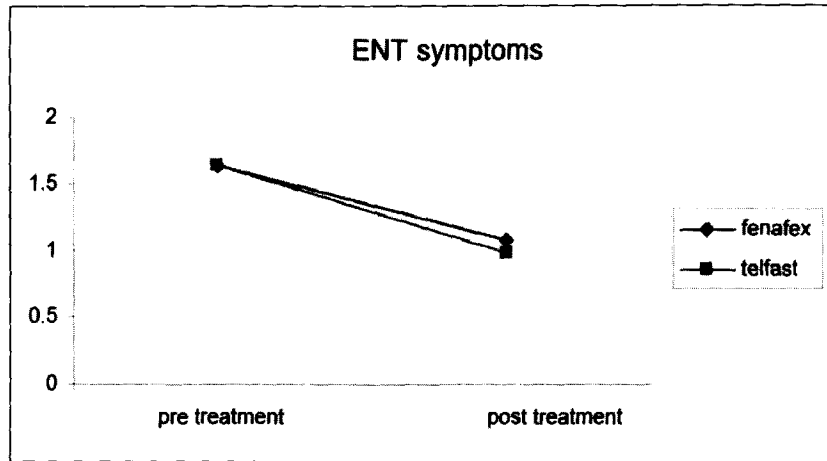


Figure 4. Pre-treatment and post-treatment otolaryngologic symptoms of local-made and original fexofenadine.

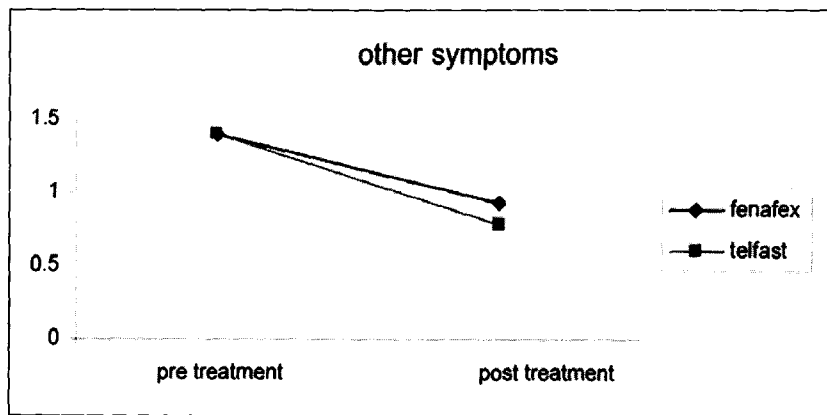


Figure 5. Pre-treatment and post-treatment other symptoms of local-made and original fexofenadine.

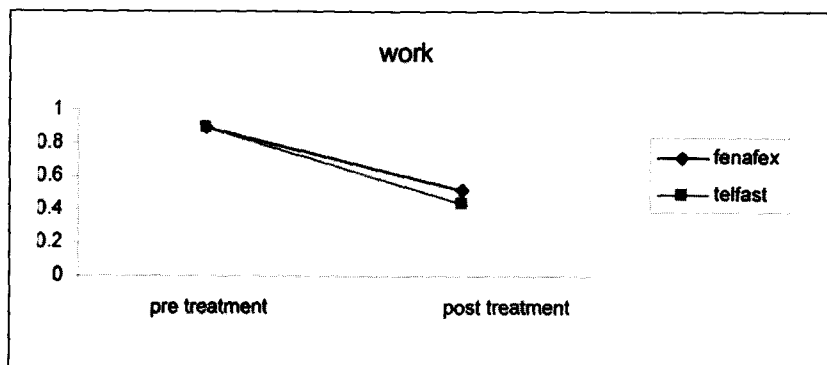


Figure 6. Pre-treatment and post-treatment work trouble of local-made and original fexofenadine.

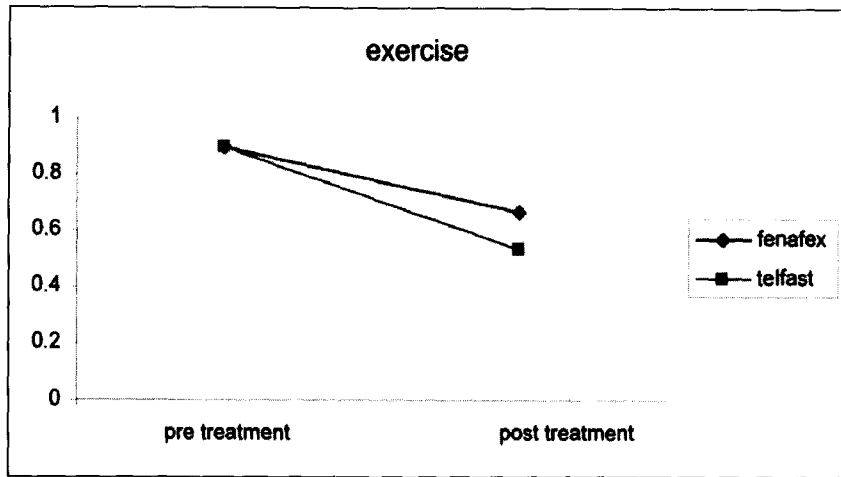


Figure 7. Pre-treatment and post-treatment exercise disability of local-made and original fexofenadine.

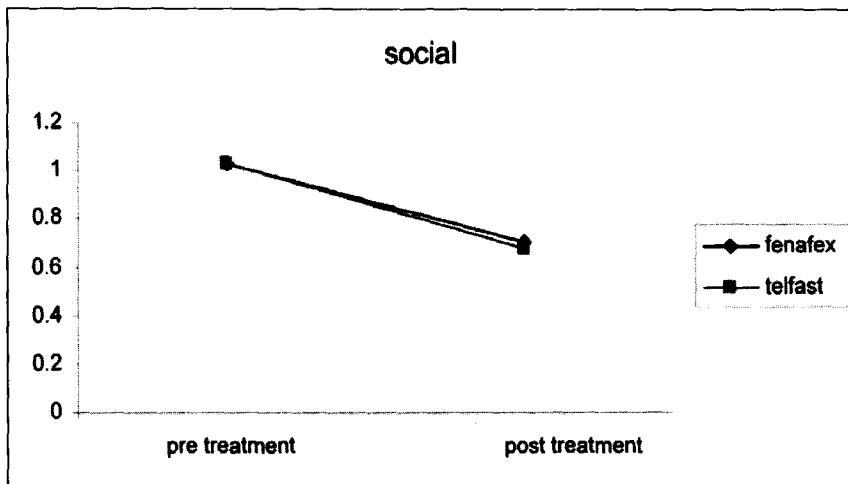


Figure 8. Pre-treatment and post-treatment sleep disturbance of local-made and original fexofenadine.

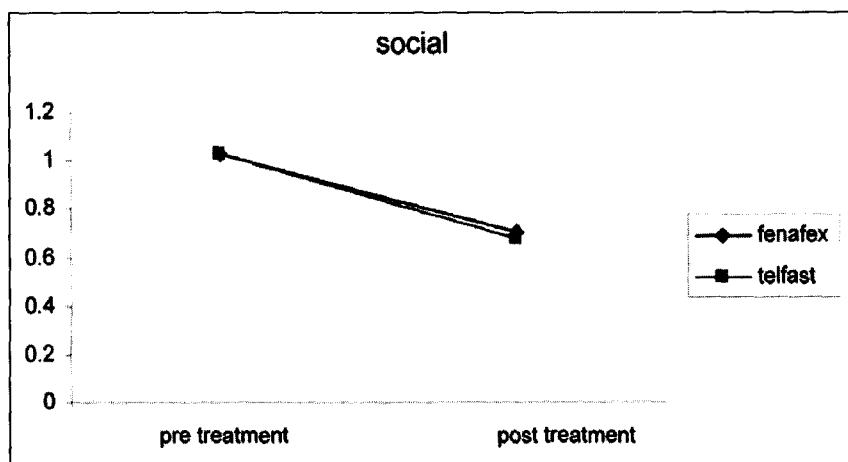


Figure 9. Pre-treatment and post-treatment social trouble of local-made and original fexofenadine.

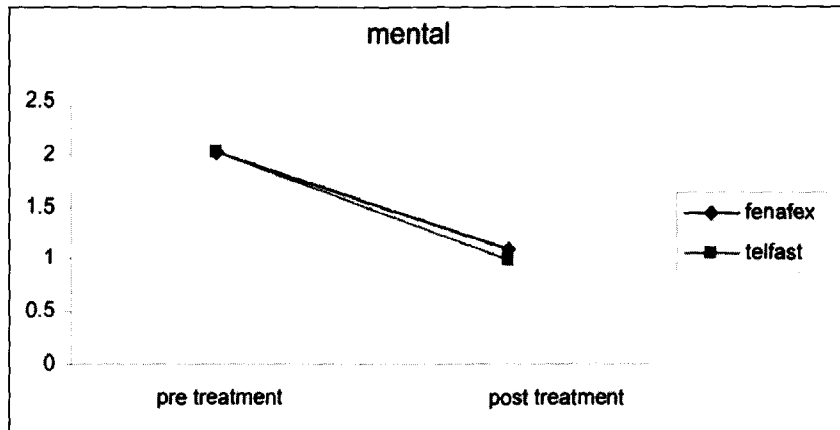


Figure 10. Pre-treatment and post-treatment emotional disturbance of local-made and original fexofenadine.

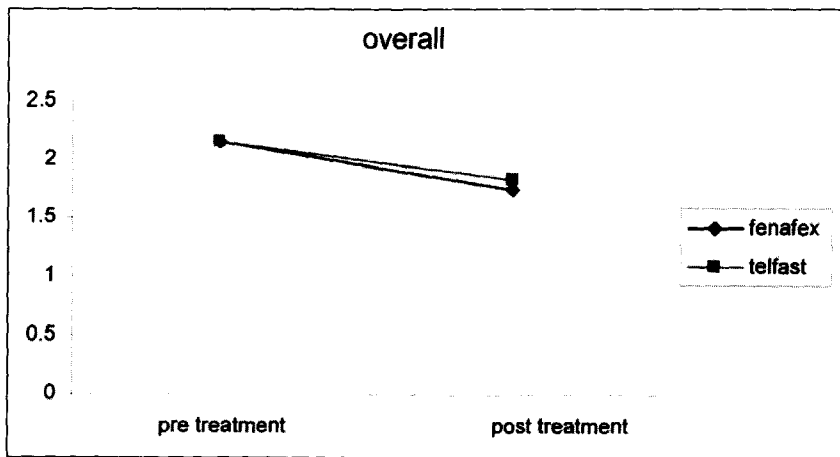


Figure 11. Pre-treatment and post-treatment general health perception of local-made and original fexofenadine.

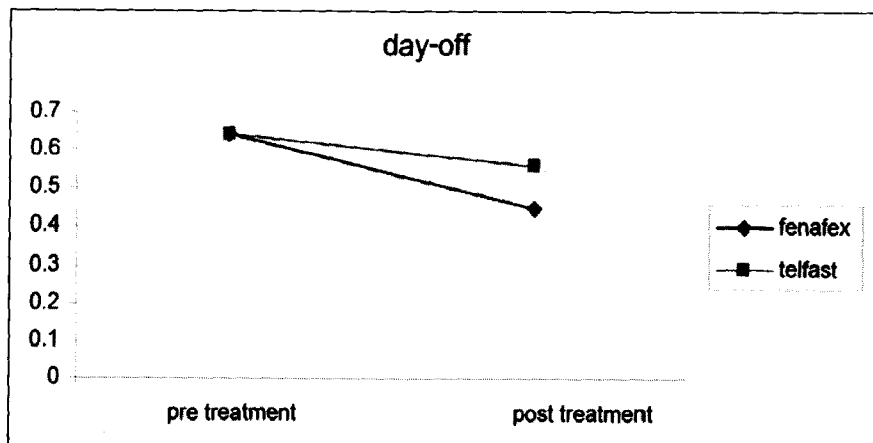


Figure 12. Pre-treatment and post-treatment work time missed of local-made and original fexofenadine.

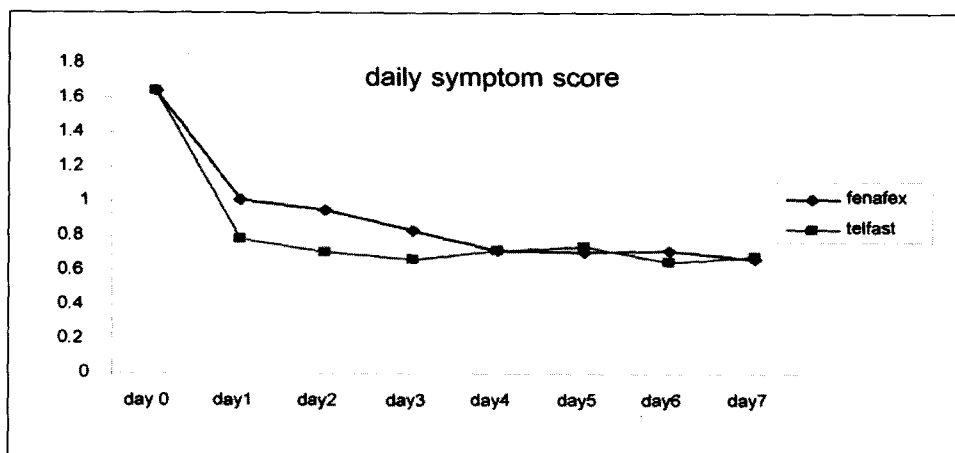


Figure 13. Daily symptoms score of the local-made and original fexofenadine.

Discussion

This trial demonstrated that both the local-made and original fexofenadine were both efficacious and safe for persistent allergic rhinitis. We decided to measure H1-blockade effect by allergen-induced wheal and flare suppression since this method should be more specific to *Dermatophagoides Pteronyssinus* than method of histamine-induced. Intradermal skin test was used as being more sensitive than skin prick test. Fexofenadine was proved by other trials to be an effective H1-receptor antagonist. It rapidly suppressed both wheal and flare, and had a faster onset of action than loratadine, compared by serial measurement of the suppressive effect of wheal and flare. ⁽⁵⁾

Antihistamines have been well known for having no effect on nasal obstruction. Our study did not see significant effect on peak nasal inspiratory flow. Patients had greater flow insignificantly from baseline. This result did not differ from some studies. Roongapinun, et al. proposed that cetirizine, fexofenadine and loratadine did not have significant effect on congestion score and nasal airway resistance. ⁽⁶⁾ Nevertheless, some still believe

fexofenadine should result in a better effect on nasal congestion than other first and second generation antihistamines since it may possess anti-inflammatory properties. Abdelaziz, et al. found that eosinophil-induced release of IL-8, GM-CSF and sICAM-1 from the human nasal epithelial cells was significantly attenuated by treatment with fexofenadine. Addition of 10^{-6} to 10^{-3} mol/L fexofenadine to the conditioned medium significantly attenuated eosinophil chemotaxis and adherence to endothelial cells. ⁽⁷⁾

Clinically, fexofenadine could reduce otolaryngologic and other symptoms continually. Bernstein, et al. assessed nasal symptoms and total symptom score after treatment with fexofenadine in ragweed seasonal allergic rhinitis and proposed the same result with our trial. ⁽⁸⁾ Meltzer, et al. studied the effect of fexofenadine on quality of life and impairment at work, in the classroom and in daily activities in seasonal allergic rhinitis. They reported an improvement in quality of life and a reduction in overall work impairment and daily activity impairment. The questionnaires used in their study assessed overall quality of life, activities, sleep, practical problems, nasal, eye and miscellaneous symptoms,

emotion, work and classroom time missed, work and classroom impairment and general health perception.

⁽⁹⁾ Our results not only demonstrated the same result but also reported improvement in two additional domains which were exercise and social activities.

The severity of adverse effects of fexofenadine, according to this trial, was mild. By scoring from 0 to 4, mean score of all effects was less than 1. Being not distributed to the CNS, fexofenadine is believed not to cause sleepiness. Dhorraintra, et al. studied CNS depressant effects of fexofenadine by using both subjective and objective tests including visual analogue scale, alertness rating scale, card sorting test, glass bead picking test, recording of the reaction time test for light stimulation. The results demonstrated no CNS side effect of both fexofenadine and placebo. ⁽¹⁰⁾

One limitation of this study was a high number of non participation. Only thirty-seven out of ninety-nine patients who were positive to *Dermatophagoides Pteronyssinus* completed the trial. This was due to many reasons; being uncertain of safety of the experiment, too frequent visits, too many investigations and much time consuming. Measures such as a fast track for participants or other privileges may bring a better cooperation for further studies.

Conclusion

The local-made fexofenadine was not significantly different from an original one (imported) regarding their efficacy in the suppression of allergen-induced wheal and flare reaction, the increase of peak nasal inspiratory flow, the decrease of clinical symptoms and the improvement of quality of life. The adverse effects of both drugs were not different.

Acknowledgements

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