

RESEARCH ARTICLES

Onset of Action, Efficacy, and Tolerability of Loratadine, Fexofenadine and Cetirizine under Nasal Allergen Challenge in Perennial Allergic Rhinitis

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Abstract

Introduction: Loratadine, Fexofenadine and Cetirizine have been widely used for allergic rhinitis. This study aimed to examine the efficacy, onset of action and tolerability of these agents under dust mite nasal challenge.

Patients and Methods: Thirty-one allergic rhinitis patients were randomly given 10 mg of loratadine (n=8), 60 mg of fexofenadine (n=8), 10 mg of cetirizine (n=8), or a placebo (n=7) after collecting the baseline. The nasal allergen challenge was repeated every 30 min after taking medication for 4 h. Total nasal symptom score (TNSS) and secretion weight were assessed ten min after each challenge. Adverse effects were evaluated hourly. Additionally, the time points with definitive relief (relative efficacy) resolved by treatments were analyzed.

Results: Antihistamines prevailed over the placebo at 120 min for cetirizine, 150 min for fexofenadine, and 180 min for loratadine. At certain points, cetirizine was more effective than loratadine on TNSS, secretion and congestion score. All drugs had a greater relative efficacy on TNSS than the placebo. Fexofenadine and cetirizine displayed a high relative efficacy. The incidence of adverse effect was high due to experimental procedure, however, it was similar among groups.

Conclusion: All drugs were more effective than the placebo. Cetirizine had the fastest onset. There was an ample significant discrepancy in efficacy among these drugs. Active agents and placebo equally affected the adverse events.

Key words : perennial allergic rhinitis; nasal allergen challenge; loratadine; fexofenadine; cetirizine

ระยะเวลาเริ่มต้นออกฤทธิ์ ประสิทธิภาพ และความสามารถทนต่อยาลอราทาเด็น ฟิโซเฟนนาเด็น และเซทอสิริซินในผู้ป่วยภูมิแพ้จมูกอักเสบชนิดเป็นตลอดปีที่ได้รับการกระดุนโพรงจมูกด้วยไรฟุ่น

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บทคัดย่อ

บทนำ ในปัจจุบันมีการนำยาลอราทาเด็น ฟิโซเฟนนาเด็น และเซทอสิริซินมาใช้อย่างแพร่หลายในการรักษาผู้ป่วยภูมิแพ้จมูกอักเสบ การศึกษานี้มีจุดประสงค์เพื่อทดสอบประสิทธิภาพ ระยะเวลาเริ่มต้นออกฤทธิ์ และความสามารถทนต่อยาดังกล่าวในผู้ป่วยที่ได้รับการกระดุนโพรงจมูกด้วยไรฟุ่น

วิธีการ หลังจากเก็บข้อมูลพื้นฐาน ผู้ป่วยภูมิแพ้จมูกอักเสบ 31 คนถูกสุ่มเพื่อรับยาลอราทาเด็น 10 มก จำนวน 8 คน ยาฟิโซเฟนนาเด็น 60 มก จำนวน 8 คน ยาเซทอสิริซิน 10 มก จำนวน 8 คน หรือไดร์บันยาหลอกจำนวน 7 คน ต่อจากนั้นผู้ป่วยได้รับการกระดุนโพรงจมูกด้วยไรฟุ่นทุก 30 นาที เป็นเวลา 4 ชั่วโมง การประเมินอาการทางจมูกและการซึ้งน้ำหนักน้ำมูกจะกระทำที่ 10 นาทีหลังการกระดุนโพรงจมูกแต่ละครั้ง ทุก 1 ชั่วโมงจะประเมินฤทธิ์ไม่พึงประสงค์จากการใช้ยา

ผลการศึกษา พบว่ายาเซทอสิริซินลดอาการรวมทางจมูกได้ดีกว่ายาหลอกที่ 120 นาที ยาฟิโซเฟนนาเด็น ลดอาการทางจมูกได้ดีกว่ายาหลอกที่ 150 นาที และยาลอราทาเด็นลดอาการทางจมูกได้ดีกว่ายาหลอกที่ 180 นาที ยาเซทอสิริซินมีประสิทธิภาพลดอาการรวมทางจมูก ปริมาณน้ำมูก และอาการคัดจมูก ดีกว่ายาลอราทาเด็นในบางช่วงเวลา การเปรียบเทียบ relative efficacy อาการรวมทางจมูก พบว่ายาทุกตัวได้ผลดีกว่ายาหลอก โดยยาฟิโซเฟนนาเด็น และเซทอสิริซินมีค่า relative efficacy สูงที่สุด ส่วนผลไม่พึงประสงค์จากการใช้ยาในแต่ละกลุ่มไม่แตกต่างกัน

สรุป ยาต้านภูมิแพ้ที่ทำการทดสอบทุกตัวมีประสิทธิภาพในการรักษาโรคภูมิแพ้จมูกอักเสบดีกว่ายาหลอก โดยยาเซทอสิริซินออกฤทธิ์เร็วที่สุด และแต่ละกลุ่มพบผลข้างเคียงจากการใช้ยาไม่แตกต่างกัน

คำสำคัญ perennial allergic rhinitis; nasal allergen challenge; loratadine; fexofenadine; cetirizine

Introduction

For years, three non-sedating antihistamines have been widely prescribed for treating allergic rhinitis in Thailand. They include fexofenadine, cetirizine, and loratadine. Some of them have been studied separately in seasonal allergic rhinitis (SAR)¹⁻³ and rhinitis⁴⁻⁵, but they were compared with each other in only one trial of SAR⁶. In Thailand where the perennial type of allergic rhinitis has been overwhelming, there were two studies carried out⁷⁻⁸. Yet, they were conducted in chronically-therapy basis without nasal allergen challenge (NAC) and included only some drugs. On the contrary, this study aimed to complete the investigation of the efficacy, onset of action, and tolerability of these three drugs during the 4 h period of NAC in patients with perennial allergic rhinitis.

Patients and Methods

This study was conducted in full compliance with the Declaration of Helsinki and the principles of Good Clinical Practice. The protocol and consent form for the study were reviewed and approved by the Research Ethical Committee of the Faculty of Medicine, Chiang Mai University. Written informed consent was obtained from all subjects prior to enrollment.

Subjects screening

The allergic rhinitis patients were included by meeting the following criteria: (1) age between 15-50 years; and (2) confirmed diagnosis of allergic rhinitis by history, physical examination and a positive skin test to house dust mite (Der p, Der f). The exclusion criteria were as follows: (1) history of severe asthmatic attack or anaphylaxis; (2) relevant septal deviation, polyps, or sinusitis that remained active; (3) history of antihistamine drug allergy; and (4) prior medications intake in a limited period of time (i.e. 1 week for decongestant, 2 weeks for non-sedating

antihistamine, and 4 weeks for topical or systemic steroid). Eligible subjects were enrolled to collect baseline data. The protocol and patient information guidelines were given.

Study design

This was a single center, randomized, double-blind, parallel, placebo-controlled trial. All patients underwent NAC to collect baseline data. Positive challenge was defined by symptoms score 5 and over plus increasing NAR by 50% from diluent value. Only positive-challenged patients were randomly given a single dose of Cetirizine at 10 mg (Zyrtec®, U.C.B., Thailand), Loratadine at 10 mg (Clarityne®, Schering-Plough/Zuellig, Thailand), Fexofenadine at 60 mg (Telfast®, Aventis/Zuellig, Thailand), or a placebo (corn starch, Vidhyasain, Thailand). All were contained in white-pink capsules. Patients and recorders were blinded from the treatment type. NACs were repeated with the highest concentration at 30 min intervals for 4 h after dosing. Assessments were collected 10 min after each NAC.

Nasal allergen challenge (NAC)

The patients underwent NAC by the disc method⁹. Following diluent (0.4% phenol in 0.9% normal saline) insertion, an increasing concentration of Der p and Der f (Allertech, Thailand) mixture was administered at 10 min intervals. The allergen discs (punched out the Whatman filter paper #1, Whatman, England) with 20 µL of extracts, were placed bilaterally for 30 seconds over inferior aspect of the inferior turbinate. To enroll only positive NAC subjects, nasal airway resistance was measured by active anterior rhinomanometry (Rhinomanometer, PC 200 ATMOS, Germany). The total NAR reading at 75 Pa of pressure gradient was based on a previous study in Thais¹⁰. Confounding factors in rhinomanometry were carefully guarded¹¹.

Assessments and endpoints

(i) Total nasal symptom score (TNSS) consisted of itching, stuffiness, sneezing count, and rhinorrhea. Patients were instructed on how to grade the severity score as follows: 0 = no symptom, 1 = symptom present but not annoying, 2 = symptom annoying but not interfering with normal activity, and 3 = symptom interfering with normal activity. The sneezing count score was 0 = no sneezing, 1 = 1-5 sneezes, 2 = 6-10 sneezes, and 3 = 11 or more sneezes¹². (ii) The relative efficacy was derived from the number of time points with 'zero' score (graded by patients) divided by the total time points of evaluation, the data were shown in percentage¹. (iii) Tissue paper for nose blowing was weighed (gram $\times 10^{-4}$) before and after use. It was always made readily available for every patients. Secretion was collected for 10 min after each NAC. (iv) Treatment - emergent adverse events were noted during the double blind treatment period, but not during the baseline period. Inquiries on the five adverse experiences (somnolence, dry mouth, headache, fatigue, nausea) were made hourly throughout the study.

Statistical analysis

Either Kruskal-Wallis test or analysis of variance (ANOVA) with post hoc analysis was performed. The statistical software used for these analyses was MedCalc version 7.14 for Windows (MedCalc Software, Mariakerke, Belgium). All comparisons were based on two-sided tests. Statistical significance was defined for all tests at $p < 0.05$.

Results

Patients

A total of 47 patients were enrolled. Of them, 31 (65.9%) met the criteria for positive NAC. They were randomly given a single dose of placebo (n=7), loratadine (n=8), cetirizine (n=8), or fexofenadine (n=8). They all continued to participate until the end of the study. Before NAC, all parameters were not significantly different among the four groups. After NAC was completed, a clear rise in all parameters was seen, but no significant difference among the baselines was detected. The demographic features and baseline are presented in Table 1.

Table 1 Demographic data of patients taking antihistamines and placebo^a

Parameters	Placebo (n=7)	Loratadine (n=8)	Fexofenadine (n=8)	Cetirizine (n=8)
age (yr)	30.2 \pm 11.6	28.6 \pm 12.3	28.7 \pm 16.2	31.5 \pm 13.5
Wt (kg)	50.1 \pm 3.5	55.9 \pm 3.2	49 \pm 5.5	52.3 \pm 4.8
M : F	3 : 4	4 : 4	4 : 4	3 : 5
Moderate to severe: mild persistence	4 : 3	4 : 4	5 : 3	5 : 3
NSS at baseline	8(6-10)	7.5 (4-11)	6.5 (5-13)	7.5(5-10)
NAR at baseline (Pa/ml/sec)	1.96 \pm 2.57	2.75 \pm 5.95	1.08 \pm 0.95	2.28 \pm 2.96
Secretion weight at baseline (g)	1.49 \pm 1.56	2.42 \pm 1.87	2.28 \pm 2.15	2.07 \pm 1.12

^aThere was no statistical significance among groups at baseline study

Effect on total nasal symptom score

Cetirizine suppressed TNSS more effectively than the placebo at 120 min (median -5 , 95%CI: -8.3 to -1.9 vs -2 , 95%CI: -5.1 to 2.8 , $p=0.01$) and afterwards. Fexofenadine inhibited TNSS more effectively than the placebo since 150 min (median -4 , 95%CI: -8.1 to -1.6 vs -2 , 95%CI: -5.7 to 3.2 , $p=0.02$). Loratadine inhibited TNSS more effectively than placebo at 180 min (median -4.5 , 95%CI: -8.5 to -0.2 vs -2 ,

95%CI: -5.6 to 2.8 , $p < 0.05$) and 240 min (median -6 , 95%CI: -10.8 to -2.2 vs -2 , 95%CI: -6.2 to -0.1 , $p < 0.01$). The effect of these agents on TNSS is presented in Fig. 1. Cetirizine also suppressed TNSS greater than loratadine during 120 - 150 min (median -5 , 95%CI: -8.3 to -1.9 vs -3 , 95%CI: -5.2 to -0.2 , $p=0.02$ and median -6 , 95%CI: -8.9 to -2.8 vs -4 , 95%CI: -6.9 to -0.5 , $p=0.02$). No significant difference was noted between cetirizine and fexofenadine or fexofenadine and loratadine.

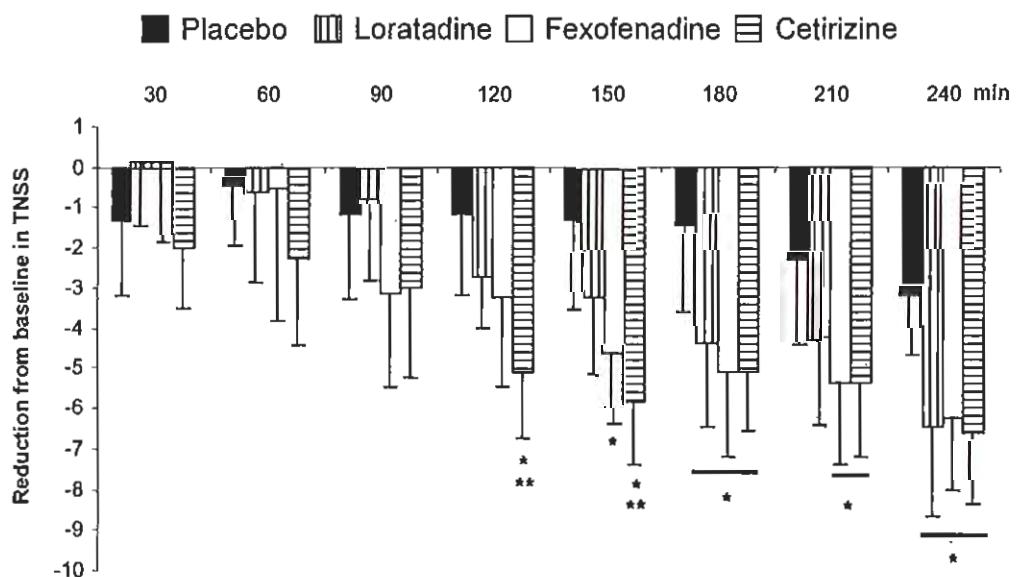


Fig. 1 Reduction in total nasal symptom score (TNSS) from baseline after treatment.
(* $p < 0.05$, compared to the placebo; ** $p < 0.05$, compared to loratadine)

Relative efficacy

Fig. 2 showed the relative efficacy in each symptom and TNSS. All active treatment groups evidenced greater relative efficacy on TNSS than the placebo group ($p < 0.05$). No statistical difference in relative efficacy of TNSS was observed among the studied drugs. Fexofenadine exhibited higher relative efficacy in the aspect of sneezing and itching score than the placebo ($p=0.01$),

whereas, cetirizine provided a superior improvement on sneezing and secretion score over the placebo ($p=0.04$). Loratadine did not clearly yield a great relative efficacy on individual symptom score than the placebo. Cetirizine and fexofenadine had a greater relative efficacy on sneezing score than loratadine ($p=0.03$). Discrepancies of cetirizine vs loratadine and cetirizine vs fexofenadine were not found.

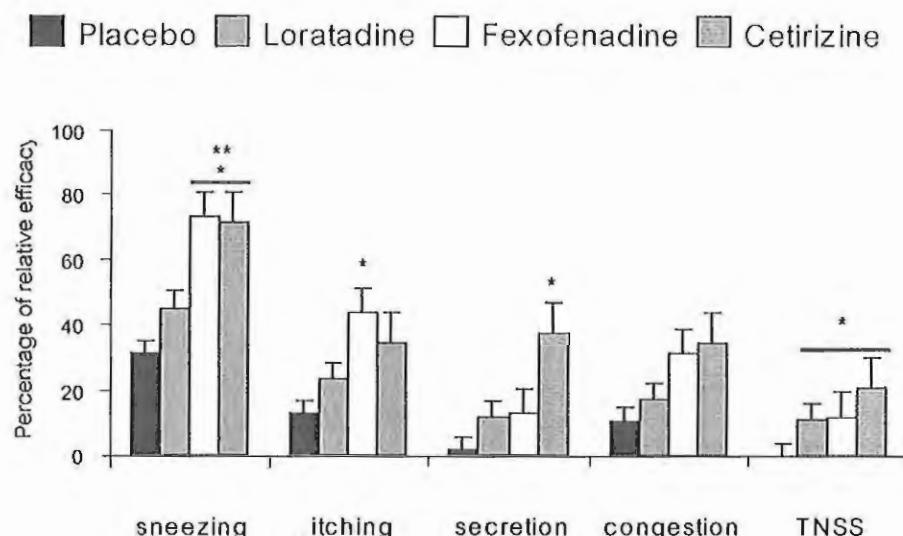


Fig. 2 Relative efficacy of the agents on individual symptom score and TNSS.
(* $p < 0.05$, compared to the placebo ; ** $p < 0.05$, compared to loratadine)

Efficacy of non-sedating antihistamines on secretion weight

All medications showed statistical differences compared to their baseline at 30, 60, 240 min for loratadine, fexofenadine, and cetirizine, respectively. Nonetheless, no antihistamine was able to reduce secretion weight significantly compared with the placebo, although all active arms inclined to do that in distal evaluations. At 210 min, the percentage reduction of secretion weight were $-54.7 \pm 61.5\%$, $-75.3 \pm 40.5\%$, $-92.2 \pm 9.9\%$, and $-85.3 \pm 15.5\%$ for the placebo, loratadine, fexofenadine, and cetirizine, respectively. At 240 min, the percentage reduction of secretion weight were -37.2 ± 96.7 , -91.4 ± 14.1 , -87.2 ± 18.6 ,

and -95.6 ± 7.8 for the placebo, loratadine, fexofenadine, and cetirizine, respectively.

Adverse experiences of non-sedating antihistamines

Study medications were well tolerated. No patient stopped treatment because of side effects or intercurrent illness. Treatment-emergent adverse events are reported in Table 2. The most common side effects were somnolence in all groups. It was found in 37.5% of each active group and 42.8% of the placebo group. The loratadine and cetirizine groups experienced another complaint such as fatigue (37.5%). However, no statistical difference on these adverse effects was detected among the groups in this study.

Table 2 Treatment-emergent adverse events for each treatment group

Drugs	n	Somnolence	Dizziness	Headache	Dry mouth	Fatigue	Nausea
Placebo	7	3 (42.9%)	2 (28.6%)	2 (28.6%)	2 (28.6%)	1 (14.3%)	0 (0.0%)
Loratadine	8	3 (37.5%)	2 (25.0%)	2 (25.0%)	2 (25.0%)	3 (37.5%)	0 (0.0%)
Fexofenadine	8	3 (37.5%)	2 (25.0%)	2 (25.0%)	2 (25.0%)	2 (25.0%)	0 (0.0%)
Cetirizine	8	3 (37.5%)	2 (25.0%)	2 (25.0%)	1 (12.5%)	3 (37.5%)	0 (0.0%)

Discussion

This is the first study which applied the disc method to longitudinally produce nasal symptoms for study the drug efficacy. We have become realized that a study of drug efficacy which conducted in community-based context would be affected by uncontrolled milieu. That is the various level of HDM in the households. As most studies have used the sophisticated allergen exposure unit; numerous factors must be considered, such as spatial distribution of allergen, air flow, calibrated ventilation system¹³. Besides, the exposure to pollens (which is larger in size than HDM excreta) are able to impair lung function¹⁴⁻¹⁶. Alternatively, nasal spray, if specifically designed to reduce fierce strike, would be another good option. However, our experience found that uncertain amount of allergen and copiously perfused extract which might interfere the secretion score must be wary. We silently applied disc to nasal mucosa. There are three studies that they showed basic elements of pathophysiology and timing-physiologic correlation underlying our implementation^{1, 6, 9, 17}.

In our model, cetirizine appeared to provide fastest relief, whereas, loratadine acted much later. This trend was supported by a number of studies¹⁻³. In this study, cetirizine exhibited more rapidly efficacious than fexofenadine. This study unveiled that the earlier recommended dose of fexofenadine (60 mg bid) might be blundered by cetirizine competitiveness, thereby, the subsequent studies tend to increase dose of fexofenadine. Cetirizine (10 mg) and higher fexofenadine (120 mg) had a comparable onset of action in alleviating the nasal symptoms in certain study¹⁸. Unluckily, the duration of action by 120 mg administration became shorter which led to introduction of highly efficacious 180 mg dose¹⁹. Notably, owing its least potency, this has allowed investigators using loratadine as comparator for any new antihistamine to study. Other authors, however, remarked that loratadine might be needed the regular use basis to encounter the effect^{20, 21}. Also, we have

already provided the underlying mechanisms which divert these agents variously²². In brief, loratadine may require a more potent metabolite (desloratadine, $T_{max} = 3-4$ h) to establish an onset²³. Cetirizine takes advantage of fexofenadine over its pharmacokinetic drawback. Since fexofenadine is a substrate for certain transporters^{24, 25}. Nonetheless, the bottom line is any studied antihistamines have been proven that every patients in the midst of allergen exposure ought to receive either of them rather than none at all.

At the end of four h, 45.8% of patients (data not shown) remained presence of symptoms despite of on therapy. Also, reflected by relative efficacy, only 10-20% of evaluated points in active treatments showed definitive relief. This emphasizes that patients taking any antihistamines without retreating themselves from allergen exposure would inevitably not be free of symptom. Probably, this explains ineffectiveness in subset of patients taking this antihistamine.

In relation to our individual score analysis (data not shown), patients would predictably respond by following sequence of onset: sneezing (120 min), secretion (120 min), pruritus (240 min). The least alleviated symptom was nasal congestion. The lack of nasal decongestant effect in the continuous HDM challenge was occasionally seen²⁶ and confirmed by our rhinomanometric study²⁷. A minimal rise of TNSS was seen in each group of cetirizine and loratadine from 150 to 210 min. This might be caused by late-phase responses which antihistamines are unable to exert a pivotal action. The fact that all three drugs possessed anti-inflammatory activity *in vitro*^{28, 29}, the importance of this activity in contributing overall clinical efficacy is not known³⁰.

In our analysis showed that secretion weight insignificantly reduced by active treatments. Although this was also observed in one study⁶, we do not recommend weighing secretion as an indicator because of nasal blockage in perennial allergic rhinitis would become a factor. Instead, nasal albumin level, which

reflected vascular leakage, was another option that was decreased by antihistamines^{31,32}.

Adverse events found in our study were exclusively high, especially somnolence (up to 37% in each group). Other studies reported fewer than 5%¹. Some reported high adverse events, but not over 33% with predominate of headache^{2,3}. Notably, the complex of fatigue, somnolence, dizziness, and headache sensationaly laps over one another and they are often problematic in study non-sedating antihistamines. Somnolence and fatigue, which were greatly experienced in this study, likely resulted from continuous nasal challenge. Rather, the use of reaction threshold method than constantly high-dose allergen exposure can relieve them³³.

Conclusion

All drugs were more effective than the placebo under an acute exposure situation. They preferably suppressed subjective hallmarks with fewer objective evaluations. The least symptom relief is nasal congestion. Cetirizine had the fastest onset. Differences among various antihistamines, other than time-to-onset, seemed to be present. Finally, all antihistamines were well tolerated.

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References

1. Day JH, Briscoe MP, Clark RH, et al. Onset of action and efficacy of terfenadine, astemizole, cetirizine, and loratadine for the relief of symptoms of allergic rhinitis. *Ann Allergy Asthma Immunol* 1997; 79(2):163-172.
2. Day JH, Briscoe M, Widlitz MD. Cetirizine, loratadine, or placebo in subjects with seasonal allergic rhinitis: effects after controlled ragweed pollen challenge in an environmental exposure unit. *J Allergy Clin Immunol* 1998; 101(5):638-645.
3. Meltzer EO, Weiler JM, Widlitz MD. Comparative outdoor study of the efficacy, onset and duration of action, and safety of cetirizine, loratadine, and placebo for seasonal allergic rhinitis. *J Allergy Clin Immunol* 1996; 97(2):617-626.
4. Nunes C, Ladeira S. Double-blind study of cetirizine and loratadine versus placebo in patients with allergic rhinitis. *J Investig Allergol Clin Immunol* 2000; 10(1):20-23.
5. Sienra-Monge JJ, Gazca-Aguilar A, Rio-Navarro B. Double-blind comparison of cetirizine and loratadine in children aged 2 to 6 years with perennial allergic rhinitis. *Am J Ther* 1999; 6(3):149-155.
6. Van Steekelenburg J, Clement PA, Beel MH. Comparison of five new antihistamines (H₁-receptor antagonists) in patients with allergic rhinitis using nasal provocation studies and skin tests. *Allergy* 2002; 57(4):346-350.
7. Bunnag C, Jareoncharssi P, Tunsuriyawong P, et al. A non-comparative trial of the efficacy and safety of fexofenadine for treatment of perennial allergic rhinitis. *Asian Pac J Allergy Immunol* 2000; 18 (3):127-133.
8. Chaweewan B, Jareonchai PDB. A clinical comparison of cetirizine versus astemizole in perennial allergic rhinitis. *Drug Investigation* 1993; 5:222-228.
9. Wagenmann M, Baroody FM, Kagey-Sobotka A, Lichtenstein LM, Naclerio RM. The effect of terfenadine on unilateral nasal challenge with allergen. *J Allergy Clin Immunol* 1994; 93(3):594-605.
10. Bunnag C, Jareoncharssi P, Dachpounpour P, et al. Nasal airway resistance in asymptomatic Thai population. *Siriraj Hosp Gaz* 1995; 47(8): 721-725.
11. Schumacher MJ. Rhinomanometry. *J Allergy Clin Immunol* 1989; 83(4):711-718.
12. Pipkorn U. Budesonide and nasal histamine challenge. *Allergy* 1982; 37(5):359-363.
13. Krug N, Hohlfeld JM, Larbig M, et al. Validation of an environmental exposure unit for controlled human inhalation studies with grass pollen in patients with seasonal allergic rhinitis. *Clin Exp Allergy*. 2003;33(12):1667-74.
14. Rosenberg GL, Rosenthal RR, Norman PS. Inhalation challenge with ragweed pollen in ragweed-sensitive asthmatics. *J Allergy Clin Immunol*. 1983;71(3):302-10.
15. Spieksma FT, Kramps JA, van der Linden AC, et al. Evidence of grass-pollen allergenic

activity in the smaller micronic atmospheric aerosol fraction. *Clin Exp Allergy*. 1990;20 (3):273-80.

16. Suphioglu C, Singh MB, Taylor P, et al. Mechanism of grass-pollen-induced asthma. *Lancet*. 1992;339(8793):569-72.
17. Wang D, Smitz J, Waterschoot S, et al. An approach to the understanding of the nasal early-phase reaction induced by nasal allergen challenge. *Allergy* 1997;52:162-7.
18. Horak F, Stubner P, Zieglmayer R, et al. Controlled comparison of the efficacy and safety of cetirizine 10 mg o.d. and fexofenadine 120 mg o.d. in reducing symptoms of seasonal allergic rhinitis. *Int Arch Allergy Immunol* 2001; 125(1):73-9.
19. Hampel F, Ratner P, Mansfield L, et al. Fexofenadine hydrochloride, 180 mg, exhibits equivalent efficacy to cetirizine, 10 mg, with less drowsiness in patients with moderate-to-severe seasonal allergic rhinitis. *Ann Allergy Asthma Immunol*. 2003; 91(4):354-61.
20. Chervinsky P, Georgitis J, Banov C, et al. Once daily loratadine versus astemizole once daily. *Ann Allergy* 1994; 73(2):109-13.
21. Del Carpio J, Kabbash L, Turenne Y, et al. Efficacy and safety of loratadine (10 mg once daily), terfenadine (60 mg twice daily), and placebo in the treatment of seasonal allergic rhinitis. *J Allergy Clin Immunol* 1989; 84:741-6.
22. Roongapinun S, Wajajamreon S, Fooanant S. Comparative efficacy of wheal-and-flare suppression among various non-sedating antihistamines and the pharmacologic insights to their efficacy. *J Med Assoc Thai*. 2004; 87(5):551-6.
23. Affrime M, Gupta S, Banfield C, Cohen A. A pharmacokinetic profile of desloratadine in healthy adults, including elderly. *Clin Pharmacokinet*. 2002;41 Suppl 1:13-9
24. Dresser GK, Bailey DG, Leake BF, et al. Fruit juices inhibit organic anion transporting polypeptide-mediated drug uptake to decrease the oral availability of fexofenadine. *Clin Pharmacol Ther*. 2002;71(1):11-20.
25. Tian R, Koyabu N, Takanaga H, et al. Effects of grapefruit juice and orange juice on the intestinal eflux of P-glycoprotein substrates. *Pharm Res*. 2002;19(6):802-9.
26. Horak F, Toth J, Hirschwehr R, et al. Effect of continuous allergen challenge on clinical symptoms and mediator release in dust-mite-allergic patients. *Allergy* 1998;53 (1):68-72.
27. Roongapinun S, Wajajamreon S, Fooanant S. A pilot study: decongestant effect of loratadine, fexofenadine, and cetirizine in perennial allergic rhinitis. *Chiang Mai Med Bull* 2003;42(2):79-88
28. Ciprandi G, Pronzato C, Ricca V, et al. Loratadine treatment of rhinitis due to pollen allergy reduces epithelial ICAM-1 expression. *Clin Exp Allergy* 1997;27 (10):1175-83.
29. Ciprandi G, Passalacqua G, Canonica GW. Effects of H1 antihistamines on adhesion molecules: a possible rationale for long-term treatment. *Clin Exp Allergy* 1999;29 Suppl 3:49-53.
30. Simons FER. Antihistamines. In: Naclerio RM, editor. Rhinitis: mechanisms and management. New York: Marcel Dekker, Inc., 1999:267-290.
31. Frossard N, Lacroix J, Melac M, et al. Onset of action in the nasal antihistaminic effect of cetirizine and loratadine in patients with allergic rhinitis. *Allergy* 1997; 52(2):205-9.
32. Frossard N, Benabdesselam O, Melac M, et al. Nasal effect of cetirizine and loratadine at 24 hours in patients with allergic rhinitis. *Am J Ther* 1998;5(5):307-11.
33. Persi L, Demoly P, Harris AG, et al. Comparison between nasal provocation tests and skin tests in patients treated with loratadine and cetirizine. *J Allergy Clin Immunol*. 1999;103(4):591-4.