Asian Biomedicine Vol. 9 No. 3 June 2015; 387 - 395 DOI: 10.5372/1905-7415.0903.408

Brief communication (Original)

Fexofenadine and levocetirizine have equivalent effectiveness for persistent allergic rhinitis

Kornkiat Snidvongs[a], Chutima Rotjanasiriphong[b], Chantima Phannaso[a], Supinda Chusakul[a], Songklot Aeumjaturapat[a]

[a]*Department of Otolaryngology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand*

[b]*Department of Otolaryngology, Maharat Nakhon Ratchasima Hospital, Nakhon Ratchasima 30000, Thailand*

Background: Antihistamines are used to treat allergic rhinitis. Whether better pharmacokinetic and pharmacodynamic properties confer higher clinical effectiveness is not known.

Objectives: To compare the effectiveness of original fexofenadine, original levocetirizine, and locally-manufactured fexofenadine for treating persistent allergic rhinitis.

Methods: Patients with persistent allergic rhinitis were enrolled during June 2010 to December 2013. Patients were allocated to receive original fexofenadine, original levocetirizine, or locally-manufactured fexofenadine for one week. Daily symptoms were self-assessed. Disease specific quality of life, allergen induced wheal and flare size, peak nasal inspiratory flow, and any adverse events were reported at one week.

Results: We enrolled 69 patients. There was no significant difference in reduction of mean total symptom score between original fexofenadine, original levocetirizine, and locally-manufactured fexofenadine (mean (95% CI); 5.52 (3.98, 7.06), 4.32 (2.43, 6.21), 4.45 (2.51, 6.40)) respectively. Improvement in otolaryngic symptoms ($P = 0.51$), nonotolaryngic symptoms ($P = 0.59$), work and study performance ($P = 0.42$), exertion ($P = 0.81$), sleep disturbance ($P = 0.76$), social disturbance ($P = 0.16$), emotional disturbance ($P = 0.66$), overall general health ($P = 0.55$), allergen induced wheal ($P = 0.44$) and flare suppression ($P = 0.90$), and peak nasal inspiratory flow ($P = 0.85$) were not significantly different between the 3 groups. All groups similarly reported minor adverse events.

Conclusions: There is no difference in effectiveness between fexofenadine and levocetirizine in treating persistent allergic rhinitis. Locally-manufactured and original fexofenadine similarly improve symptoms, nasal air flow, and quality of life. No major drug-related adverse events were reported.

Keywords: allergic rhinitis, H_1 antagonists, antihistamines, fexofenadine, levocetirizine, local-manufactured drugs, generic

Third generation antihistamines (H_1-receptor antagonists) are active enantiomers or metabolite derivatives of second generation drugs. They are widely used for treating allergic rhinitis because of their advantages over second generation antihistamines. Their anti-inflammatory properties have been reported [1, 2]. As active metabolites, they do not pass hepatic metabolism, and therefore have fewer adverse effects and do not have drug interactions with macrolides. No clinically significant cardiac effects have been reported for the new generation H_1 antihistamines, while astemizole and terfenadine have been removed from the market in most countries because of their potential to the prolong QT interval, and cause serious polymorphic ventricular arrhythmias, such as torsades de pointes [3].

Various types of H_1-receptor antagonists have various pharmacokinetic and pharmacodynamics properties. To date, fexofenadine, levocetirizine, and desloratadine are considered third generation antihistamines. Each drug has an advantage over the others. Among these three, desloratadine has the highest affinity for binding receptors [4], the longest half-life, and lowest elimination rate [4, 5]. Fexofenadine has the lowest percentage of plasma protein binding [4]. Therefore, the plasma concentration of free drug should be the highest for

Correspondence to: Kornkiat Snidvongs, Department of Otolaryngology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand. E-mail: drkornkiat@yahoo.com

fexofenadine. Levocetirizine has the lowest volume of distribution, which means its concentration is lowest in the tissue and highest in the extracellular space around the H_1 receptors [4]. The time to maximal concentration and the onset of action is modestly shorter for levocetirizine [5]. The effect duration of the third generation antihistamines of about 24 hours is considered similar [5]. However, whether better pharmacokinetic and pharmacodynamic properties confer higher clinical effectiveness is not known. There is one study by Horak and colleagues reporting greater effectiveness of levocetirizine over fexofenadine in alleviating seasonal allergic rhinitis symptoms of patients with grass pollen exposure [6]. However, the issue remains controversial. To date, there are no studies comparing third generation antihistamines in treating persistent perennial allergic rhinitis.

Locally-manufactured drugs are approved by The Thai Food Drug Administration when they have similar pharmacokinetic and pharmacodynamic properties to the original. Although available in the market, it is not evident to clinicians whether their clinical effectiveness is comparable. We aimed to compare the effectiveness of fexofenadine versus levocetirizine for treating patients with persistent allergic rhinitis, and compared the effectiveness of locally-manufactured and original fexofenadine.

Materials and methods

Study design

This controlled bioequivalence study was conducted at King Chulalongkorn Memorial Hospital. All patient participants provided written informed consent before their participation in the study. This study was approved by the Institutional Review Board of Faculty of Medicine, Chulalongkorn University. The project was funded by SPS Medical Company (Klongsan, Bangkok, Thailand). However, SPS Medical Company was not involved in the study design, data collection, or manuscript preparation. The decision of publication is based solely on the authors' consideration.

Patients

Patients with persistent allergic rhinitis who visited King Chulalongkorn Memorial Hospital from June 2010 to December 2011 were enrolled. The diagnostic criteria for persistent allergic rhinitis followed the classification of Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 [7]. The eligibility criteria included adults, aged between 18 to 60 years old, diagnosed with persistent allergic rhinitis, having skin prick test positive to *Dermatophagoides pteronyssinus*, and being healthy without any chronic underlying diseases. Exclusion criteria included dermatographism, active rhinosinusitis, pregnancy, lactation, having any psychiatric problems, having immunotherapy during the past two years, current use of a long acting β agonist, tricyclic antidepressant, corticosteroid, topical nasal drugs, and having a history of allergy to antihistamines. All participants received information regarding the objectives, methods of the study, and possible adverse effects of fexofenadine and levocetirizine. They were requested to stop using antihistamines, antileukotrienes, oral decongestants, and topical corticosteroids for two weeks and oral corticosteroids for four weeks before and during the study.

Allocation and blinding

Patients were allocated into three groups to receive original fexofenadine 180 mg (Telfast, Sanofi, Paris, France), original levocetirizine 5 mg (Xyzal, GlaxoSmithKline, Brentford, London, UK) or locally-manufactured fexofenadine 180 mg (Fenafex, SPS Medical Company, Bangkok, Thailand). All drugs were purchased from the same pharmacy and put into capsules. All capsules had identical appearance without a label. The process of randomization, allocation concealment, and blinding was done by the third author (CP) who is not a treating physician and was not involved in the assessment of outcomes. When the patients were enrolled, sealed envelopes indicating their allocation were opened. Patients then were assigned to interventions and took medicine once daily in the morning for one week. The patients, doctors, and outcome assessors were blinded to the assignment.

Outcomes

The primary outcome of this study was total symptom score. Symptoms reported were rhinorrhea, itchy nose, nasal obstruction, sneezing, cough, dry mouth, and phlegm, and were scored from 0 to 4. Score 0 means having no symptoms or no trouble and score 4 means highest degree of symptom/trouble severity. The total symptom score is the first domain of The Quality of Life Questionnaire of Allergic Rhinoconjunctivitis (Rcq-36). It was scored by the patients at baseline and the endpoint at one week. In

addition, patients daily assessed the total symptom score and any adverse events twice a day, once in the morning and once in the afternoon. The mean daily total symptom score were calculated for analysis.

The secondary outcomes were other domains of the Rcq-36, which were nonotolaryngic symptoms, work and study performance, exertion, sleep disturbance, social disturbance, emotional disturbance, and overall general health. Peak nasal inspiratory flow (PNIF), allergen-induced wheal and flare suppression, and adverse events were also reported. PNIF was measured by using In-Check Nasal (Clement Clarke International, Harlow, Essex, UK. It was measured three times and the highest value was recorded. Wheal and flare was induced by intradermal injection with 0.01 mL of a 1:12,500 dilution of *Dermatophagoides pteronyssinus* extract. The Quality of Life Questionnaire Rcq-36, PNIF, and allergen induced wheal and flare were measured at baseline and the endpoint at one week.

Statistical analysis

Analyses were performed on the intent-to-treat population, which was defined as all patients who were allocated and given subsequent treatment. Descriptive parametric data are presented as number, percentage, mean, and standard deviation (SD). Comparative data were presented as mean (95% CI). An ANOVA was used to compare the change in mean total symptom score, quality of life, wheal, flare, and PNIF between groups. A Bonferroni test was used for post hoc pair comparisons. A paired *t* test was used for comparisons between baseline and post-treatment outcomes. A chi-square test was used for cross-tab analysis between drugs and adverse events. $P < 0.05$ was considered significant. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp, Armonk, NY, USA).

Results

Patient population

There were 131 patients assessed for eligibility criteria and 69 patients enrolled. No patients were lost to follow up or discontinued the study. There were 41 women (70%). The mean age of the patients was 34.1 ± 11.1 years. Twenty-two (32%), 25 (36%), and 22 (32%) patients received original fexofenadine, original levocetirizine, and locally-manufactured fexofenadine respectively. Demographic data is shown in **Table 1**.

Outcomes

When compared to baseline, original fexofenadine ((mean (95%CI)) 9.50 (7.19, 11.8)) versus 5.05 (3.42, 6.67), $P < 0.001$), original levocetirizine (10.80 (9.37, 12.23) versus 5.28 (4.21, 6.35), $P < 0.001$) and locally-manufactured fexofenadine (10.18 (7.99, 12.37) versus 5.86 (4.83, 6.90), $P < 0.001$), decreased post-treatment total symptom scores significantly. When compared between the 3 groups, there was no significant difference in the improvement in total symptom score (original fexofenadine, original levocetirizine, and locally-manufactured fexofenadine: 4.45 (2.51, 6.40), 5.52 (3.98, 7.06), 4.32 (2.43, 6.21) respectively; $P = 0.55$). Data are shown in **Table 2**. All groups improved total symptom scores within one day. There was no difference between the groups on the first day or throughout. There was no serious (reportable) study-related adverse event.

Table 1. Demographic data of the patient participants by treatment group

	Original fexofenadine (n = 22)	Original levocetirizine (n = 25)	Locally-manufactured fexofenadine (n = 22)
Age (years)	32.3 ± 9.3	32.6 ± 11.3	37.6 ± 12.2
Female (%)	69	72	68
Duration (years)	8.2 ± 7.6	7.3 ± 6.3	7.0 ± 6.5
Mild (%)	77	72	59
Moderate to severe (%)	23	28	41

Data are presented as percentage and mean ± SD. Duration refers to persistent allergic rhinitis

Table 2. Baseline, post-treatment, and improvement in total symptom score, disease-specific quality of life, PNIF, allergen-induced wheal and flare size

	O Fexo (n = 22)	O Levo (n = 25)	L Fexo (n = 22)	Comparison three groups (*P*)	O Fexo versus O Levo (*P*)	O Fexo versus L Fexo (*P*)	O Levo versus L Fexo (*P*)
Total symptom score (mean (95% CI))							
Baseline	9.50 (7.19,11.81)	10.80 (9.37,12.23)	10.18 (7.99,12.37)	0.62	1.00	1.00	1.00
Post-treatment	5.05 (3.42,6.67)	5.28 (4.21,6.35)	5.86 (4.83,6.90)	0.63	1.00	1.00	1.00
Change	4.45 (2.51,6.40)	5.52 (3.98,7.06)	4.32 (2.43,6.21)	0.55	1.00	1.00	0.96
Nonotolaryngic symptoms (mean (95% CI))							
Baseline	13.77 (9.74,17.81)	12.88 (10.20,15.56)	12.27 (9.65,14.89)	0.79	1.00	1.00	1.00
Post-treatment	7.59 (4.09,11.09)	5.68 (3.82,7.54)	6.95 (4.17,9.74)	0.57	1.00	0.91	1.00
Change	6.18 (3.44,8.92)	7.20 (4.41,9.99)	5.32 (2.82,7.82)	0.59	1.00	1.00	0.92
Work and study performance (mean (95% CI))							
Baseline	1.86 (1.01,2.72)	2.60 (1.53,3.67)	1.91 (1.20,2.62)	0.40	0.71	1.00	0.80
Post-treatment	0.91 (0.24,1.58)	1.00 (0.29,1.71)	0.91 (0.42,1.40)	0.97	1.00	1.00	1.00
Change	0.95 (0.34,1.57)	1.60 (0.55,2.65)	1.00 (0.42,1.58)	0.42	0.73	1.00	0.84
Exertion (mean (95% CI))							
Baseline	2.55 (1.51,3.59)	2.04 (0.92,3.16)	2.36 (1.37,3.36)	0.77	1.00	1.00	1.00
Post-treatment	1.23 (0.44,2.01)	0.88 (0.18,1.58)	1.45 (0.57,2.34)	0.55	1.00	1.00	0.85
Change	1.32 (0.50,2.13)	1.16 (0.42,1.90)	0.91 (0.24,2.06)	0.81	1.00	1.00	1.00
Sleep disturbance (mean (95% CI))							
Baseline	3.59 (2.23,4.95)	4.04 (2.86,5.22)	4.36 (2.99,5.74)	0.69	1.00	1.00	1.00
Post-treatment	1.55 (0.84,2.25)	1.76 (0.73,2.79)	1.73 (0.85,2.61)	0.93	1.00	1.00	1.00
Change	2.05 (1.04,3.06)	2.28 (1.12,3.44)	2.64 (1.42,3.85)	0.76	1.00	1.00	1.00

Table 2. Baseline, post-treatment, and improvement in total symptom score, disease-specific quality of life, PNIF, allergen-induced wheal and flare size (Continuous)

	O Fexo (n = 22)	O Levo (n = 25)	L Fexo (n = 22)	Comparison three groups (*P*)	O Fexo versus O Levo (*P*)	O Fexo versus L Fexo (*P*)	O Levo versus L Fexo (*P*)
Social disturbance (mean (95% CI))							
Baseline	1.82 (0.73,2.91)	2.80 (1.62,3.98)	2.68 (1.45,3.92)	0.42	0.66	0.89	1.00
Post-treatment	1.14 (0.37,1.90)	1.52 (0.57,2.47)	0.86 (0.28,1.45)	0.48	1.00	1.00	0.69
Change	1.82 (0.83,2.80)	1.28 (0.39,2.17)	1.82 (0.83,2.80)	0.16	0.88	1.17	1.00
Emotional disturbance (mean(95%CI))							
Baseline	6.41 (4.15,8.67)	7.88 (5.63,10.13)	8.14 (5.58,10.70)	0.52	1.00	0.89	1.00
Post-treatment	2.77 (1.56,3.98)	3.60 (2.05,5.15)	3.23 (1.85,4.60)	0.69	1.00	1.00	1.00
Change	3.64 (1.92,5.35)	4.28 (2.17,6.39)	4.91 (2.80,7.02)	0.66	1.00	1.00	1.00
Overall general health (mean (95% CI))							
Baseline	2.14 (1.77,2.51)	2.08 (1.74,2.42)	1.77 (1.41,2.13)	0.29	1.00	0.44	0.61
Post-treatment	2.50 (2.17,2.83)	2.68 (2.42,2.94)	2.14 (1.89,2.38)	0.02	1.00	0.20	0.02
Change	0.36 (–0.01,0.74)	0.60 (0.22,0.98)	0.36 (0.01,0.71)	0.55	1.00	1.00	1.00
PNIF (L/min) (mean (95% CI))							
Baseline	93.86 (79.06,108.66)	92.71 (80.70,104.72)	92.27 (78.85,105.69)	0.98	1.00	1.00	1.00
Post-treatment	93.86 (75.23,112.50)	92.20 (81.51,102.89)	90.91 (78.68,103.14)	0.96	1.00	1.00	1.00
Change	0 (–9.25,9.25) (17.74,28.35)	3.20 (–11.84,18.24) (20.60,28.04)	–1.36 (–11.23,8.51) (18.05,28.68)	0.85	1.00	1.00	1.00
Change	–12.27 (–19.05, –5.49)	–13.52 (–18.61, –8.43)	–14.09 (–19.95, –8.23)	0.90	1.00	1.00	1.00

Table 2. Baseline, post-treatment, and improvement in total symptom score, disease-specific quality of life, PNIF, allergen-induced wheal and flare size (Continuous)

	O Fexo (n = 22)	O Levo (n = 25)	L Fexo (n = 22)	Comparison three groups (*P*)	O Fexo versus O Levo (*P*)	O Fexo versus L Fexo (*P*)	O Levo versus L Fexo (*P*)
Wheal size (mm) (mean (95% CI))							
Baseline	11.36 (9.44,13.29)	14.04 (11.64,16.44)	14.00 (9.56,18.44)	0.29	0.68	0.42	1.00
Post-treatment	8.91 (7.04,10.78)	10.24 (8.52,11.96)	9.77 (7.36,12.18)	0.61	1.00	0.99	1.00
Change	–2.45 (–4.56, –0.55)	–4.24 (–6.50, –1.98)	–4.23 (–6.95, –1.51)	0.44	0.83	0.77	1.00
Flare size (mm) (mean (95% CI))							
Baseline	35.32 (29.94,40.69)	38.58 (33.11,44.05)	37.45 (28.79,46.12)	0.84	1.00	1.00	1.00
Post-treatment	23.05 (17.74,28.35)	24.32 (20.60,28.04)	23.36 (18.05,28.68)	0.92	1.00	1.00	1.00
Change	–12.27 (–19.05, –5.49)	–13.52 (–18.61, –8.43)	–14.09 (–19.95, –8.23)	0.90	1.00	1.00	1.00

O Fexo = original fexofenadine, O Levo = original levocetirizine, L Fexo = locally-manufactured levocetirizine, PNIF = peak nasal inspiratory flow, mm = millimeters

Improvement in otolaryngic symptoms, nonotolaryngic symptoms, work and study performance, exertion, sleep disturbance, social disturbance, emotional disturbance, overall general health, allergen induced wheal and flare size, and peak nasal inspiratory flow were not significantly different between the 3 groups. Data are shown in Table2. However, the post-treatment PNIF was not different from baseline in all groups (original fexofenadine; 93.86 versus 93.86, $P = 1.00$, original levocetirizine; 92.20 versus 92.71, $P = 0.60$, locally-manufactured fexofenadine; 90.91 versus 92.27, $P = 0.78$.

Patients reported adverse events that were not significantly different between the 3 groups. Those events were sleepiness, dizziness, nausea, dyspepsia, fatigue, and skin rash. Data are shown in **Table 3**.

Discussion

Although the pharmacokinetics and pharmacodynamics for the various H_1-receptor antagonists differ, we found that fexofenadine and levocetirizine have similar effectiveness for symptom control and disease-specific quality of life. Moreover, when a skin-prick test was assessed, the wheal and flare suppression was found not significantly different. In theory, pharmacokinetic and pharmacodynamics properties may contribute to clinical effectiveness. Ideal H_1-receptor antagonists are expected to have low plasma-protein binding with high free drug concentration, a low volume of distribution with high drug concentration in the extracellular space around the H_1 receptors, and high affinity for H_1 receptors. Fexofenadine is known for its lower percentage of plasma protein binding [4], while levocetirizine is known for its lower volume of distribution [8]. Therefore, when several individual pharmacokinetic and pharmacodynamics parameters have been integrated, the receptor occupancy of both drugs may not be significantly different, resulting in similar clinical effectiveness, based on the results of this study.

Fexofenadine and levocetirizine have been compared in previous studies. Most studies compared their efficacy on wheal and flare suppression [9-12] or compared the overall patient satisfaction using a noninterventional observation study [13]. To our knowledge, this is the first study directly comparing the clinical effectiveness of fexofenadine and levocetirizine in patients with perennial allergic rhinitis. Patients in this study were allergic to *Dermatophagoides pteronyssinus*. We focused on this patient subgroup because seasonal allergic rhinitis is less common than perennial rhinitis in Thailand, and a comparison between fexofenadine and levocetirizine in treating seasonal allergic rhinitis has already been made by Horak et al. Additionally we focused on patients with persistent allergic rhinitis because a clinical difference between two drugs may not be seen when investigating patients with intermittent symptoms. By contrast with the present study, Horak et al. reported a longer duration of action of levocetirizine [6]. However, Horak et al. reported nasal symptoms after only a single drug administration, which may not reflect actual practice in which physicians usually prescribe H_1-receptor antagonists to patients for at least one week, particularly patients with persistent symptoms. In addition, although significantly different, the mean score difference of 1.3 (95% CI 0.7, 1.9) reported by Horak et al. may not be clinically important.

Nasal obstruction is basically the least responsive symptom to H_1-receptor antagonists for patients with persistent allergic rhinitis. New generation antihistamines may be more efficacious for controlling nasal obstruction when compared to first generation drugs because of their anti-inflammatory profile by inactivating nuclear factor κB, an important transcription factor [1]. However, our study fails to find a significant improvement of PNIF in any study group. By contrast with our findings, desloratadine, fexofenadine, and levocetirizine have been reported efficacious in relieving the nasal congestion associated

Table 3. Number of patients reporting adverse events

	O Fexo (n = 22)	O Levo (n = 25)	L Fexo (n = 22)	*P*
Sleepiness	8	16	12	0.15
Dizziness	3	8	3	0.21
Nausea	1	2	3	0.52
Dyspepsia	3	5	6	0.48
Fatigue	4	6	6	0.72
Rash	1	2	3	0.52

O Fexo = original fexofenadine, O Levo = original levocetirizine, L Fexo = locally-manufactured levocetirizine

with allergic rhinitis [14-17]. One explanation for our patients having no improvement on post-treatment PNIF is that any chronic condition of the nasal mucosa, including persistent allergic rhinitis may lead to fibrosis of the nasal epithelium because of a chronic inflammatory response [18], and this would then cause a decreased response to any medication including new generation antihistamines or even topical decongestants [19].

Locally-manufactured fexofenadine was reported in this study as having similar effectiveness to original fexofenadine. This is in concordance with a previous study by our group [20]. When locally-manufactured drugs have similar pharmacokinetic and pharmacodynamic properties to the original, they possibly have similar clinical effectiveness. However, this quality cannot applied to any kind of locally-manufactured drug available in the market. There are several other contributing factors other than pharmacokinetics and pharmacodynamics, including base formulation and purification, that may affect clinical effectiveness.

A limitation of this study is that we could not control all confounders that may affect clinical outcomes. Patients allergic to mites may be free of symptoms when their environment has been adjusted, and their symptoms may be troublesome when they live with mites in a dusty environment. In addition, some patients may be allergic to multiple allergens. Clinical outcomes will significantly correlate with exposure to those allergens.

Conclusion

H_1-receptor antagonists are effective and safe in treating patients with persistent allergic rhinitis. Patients have decreased nasal symptoms and improved quality of life after treatment. It is not yet evident whether original fexofenadine is superior to either local-manufactured fexofenadine or levocetirizine in clinical effectiveness and safety. Any adverse events reported were minor.

Acknowledgements

We thank Mahidol University, the owner, and Professor Chaweewan Boonnag, the creator, of The Quality of Life Questionnaires of Allergic Rhinoconjuntivitis (Rcq-36) for their kind permission to use the Rcq-36. We thank SPS Medical Company for the financial support of this study, although we had full access to all of the data in this study and we take complete responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of interest statement

CR has no conflict of interest to declare. KS, CP, SC, and SA have received payments for their involvement in speakers' bureaus for pharmaceutical companies including Merck Sharp and Dohme, GSK, Takeda, Sanofi Aventis, Bayer, DKSH, and Wellgate.

References

1. Bakker RA, Schoonus SB, Smit MJ, Timmerman H, Leurs R. Histamine H_1-receptor activation of nuclear factor-κB: roles for Gβγ- and $G\alpha_{q/11}$-subunits in constitutive and agonist-mediated signaling. Mol Pharmacol. 2001; 60:1133-42.
2. Leurs R, Church MK, Taglialatela M. H_1-antihistamines: inverse agonism, anti-inflammatory actions and cardiac effects. Clin Exp Allergy. 2002; 32:489-98.
3. Church DS, Church MK. Pharmacology of antihistamines. World Allergy Organ J. 2011; 4:S22-7.
4. Gillard M, Benedetti MS, Chatelain P, Baltes E. Histamine H_1 receptor occupancy and pharmacodynamics of second generation H_1-antihistamines. Inflamm Res. 2005; 54:367-9.
5. Simons FER, Simons KJ. H_1 antihistamines: current status and future directions. World Allergy Organ J. 2008; 1:145-55.
6. Horak F, Zieglmayer PU, Zieglmayer R, Kavina A, Lemell P. Levocetirizine has a longer duration of action on improving total nasal symptoms score than fexofenadine after single administration. Br J Clin Pharmacol. 2005; 60:24-31.
7. Bousquet J, Khaltaev N, Cruz AA, et al. Allergic rhinitis and its impact on asthma (ARIA) 2008 (in collaboration with the World Health Organization, GA²LEN, and AllerGen). Allergy. 2008; 63:8-160.
8. Devillier P, Roche N, Faisy C. Clinical pharmacokinetics and pharmacodynamics of desloratadine, fexofenadine and levocetirizine : a comparative review. Clin Pharmacokinet. 2008; 47:217-30.
9. Schoepke N, Church MK, Maurer M. The inhibition by levocetirizine and fexofenadine of the histamine-induced wheal and flare response in healthy Caucasian and Japanese volunteers. Acta Derm Venereol. 2013; 93:286-93.
10. Dhanya NB, Thasleem Z, Rai R, Srinivas CR. Comparative efficacy of levocetirizine, desloratidine and fexofenadine by histamine wheal suppression test. Indian J Dermatol Venereol Leprol. 2008; 74:361-3.

11. Kruszewski J, Klos K, Sulek K. [Inhibition of histamine-induced wheel after a recommended single dose administration of 10 mg cetirizine, 5 mg desloratadine, 120 i 180 mg fexofenadine, 5 mg levocetirizine and 10 mg loratadine—a randomized, double-blind, placebo controlled trial]. Pol Merkur Lekarski. 2006; 21:443-8. [in Polish]
12. Grant JA, Riethuisen JM, Moulaert B, DeVos C. A double-blind, randomized, single-dose, crossover comparison of levocetirizine with ebastine, fexofenadine, loratadine, mizolastine, and placebo: suppression of histamine-induced wheal-and-flare response during 24 hours in healthy male subjects. Ann Allergy Asthma Immunol. 2002; 88:190-7.
13. De Vos C, Mitchev K, Pinelli ME, Derde MP, Boev R. Non-interventional study comparing treatment satisfaction in patients treated with antihistamines. Clin Drug Investig. 2008; 28:221-30.
14. Bachert C. A review of the efficacy of desloratadine, fexofenadine, and levocetirizine in the treatment of nasal congestion in patients with allergic rhinitis. Clin Ther. 2009; 31:921-44.
15. Lee DK, Gardiner M, Haggart K, Fujihara S, Lipworth BJ. Comparative effects of desloratadine, fexofenadine, and levocetirizine on nasal adenosine monophosphate challenge in patients with perennial allergic rhinitis. Clin Exp Allergy. 2004; 34:650-3.
16. Ciprandi G, Cirillo I, Vizzaccaro A, Tosca MA. Levocetirizine improves nasal obstruction and modulates cytokine pattern in patients with seasonal allergic rhinitis: a pilot study. Clin Exp Allergy. 2004; 34:958-64.
17. Agrawal DK. Anti-inflammatory properties of desloratadine. Clin Exp Allergy. 2004; 34:1342-8.
18. Schmidt J, Zalewski P, Olszewski J, Olszewska-Ziaber A. Histopathological verification of clinical indications to partial inferior turbinectomy. Rhinology. 2001; 39: 147-50.
19. Williams RG, Eccles R. Nasal airflow asymmetry and the effects of a topical nasal decongestant. Rhinology. 1992; 30:277-82.
20. Snidvongs K, Saengpanich S, Aeumjaturapat S, Phannaso C. Comparative study between the efficacy of local-made and original fexofenadine in persistent allergic rhinitis. Chula Med J. 2007; 51:289-302.