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Influence of levocetirizine on the clinical course of pollen allergic rhinitis

Allergic rhinitis is a complex of symptoms caused most frequently by IgE-dependent inflammatory reaction of nasal mucous membrane in response to inhaled allergen (13, 16). In case of pollen allergic rhinitis (PAR), grass, trees or weeds/bushes pollens are responsible for clinical symptoms of this disease (3, 21). Typical symptoms observed in the acute phase of PAR are mainly caused by histamine: serous rhinitis, the feeling of a blocked nose, itching and scratching of the throat, sneezing attacks, itching and lacrimation of the eyes. In some patients, dyspnoea attacks of bronchial origin are also observed (16). These symptoms are often accompanied by headaches, fatigue, fever and problems with concentration (22). PAR treatment consists of: avoiding allergen, symptomatic treatment (pharmacotherapy) and specific immunotherapy. Allergen elimination is the most efficient and the safest method of treatment, but, in PAR, it cannot be followed because of omnipresence of pollens (23). Specific immunotherapy, together with anti-IgE antibodies, is the only causal treatment of allergy, especially effective in case of PAR (7, 9, 19). Antihistaminics and glycocorticosteroids are basic drugs used in symptomatic treatment. Antihistaminics inhibit interaction between histamine and H1 receptor that leads to elimination of most symptoms of PAR. High clinical effectiveness of antihistaminics of II generation, combined with their safety, makes them the "first choice" drug in PAR treatment, both in children and in adults (4, 19, 21, 24). Levocetirizine (LCZ), which is an active R- enantiomer of cetirizine, is one of the representants of the latest antihistaminics of II generation (2).

The aim of the study was to estimate clinical efficacy of LCZ in patients suffering from PAR.

MATERIAL AND METHODS

Patients with PAR, treated in Allergology Outpatients Clinic, fulfilling the following conditions, were qualified to this study: age 18–35 years, symptoms of moderate or severe PAR lasting for at least 2 years, positive results of skin prick tests against grass pollen allergens or/and presence of specific IgE in serum, written agreement on participating in the study. 39 patients: 20 females and 19 males were included in this study. Average age was 25.5 years, average time of PAR symptoms presence – 9.7 years. The intensity of nasal symptoms of PAR was evaluated by patients in a 10-grade visual-analogue scale, taking into consideration the following clinical symptoms: nasal congestion, sneezing,

rhinorrhea and itching of the nose. Moreover, measurements of nasal peak inspiratory flow (NPIF) were performed using the measurer (peakflowmeter) of inspiratory flow with nasal mask, produced by Clement-Clarke (8). Patients were examined three times: the first visit (V-1) took place before the beginning of grass pollen season, during asymptomatic period, the second (V-2) - during the exacerbation of nasal symptoms, in the peak of pollen season. During this visit, patients were divided into two groups – treated with levocetirizine - LCZ group (Xyzal, tablets 5mg, n = 20), or – receiving placebo – Control group (Placebo tablets, n = 19).

LCZ and placebo were both administered once daily. Finally, the last visit (V-3) took place after a 4-week period of therapy. During all the time of the study, patients were permitted to use only intranasal alpha-mimetics. During each visit, patients graded PAR symptoms from last 3 days in the visual-analogue point scale (first rank variables) and NPIF measurement was also performed (second rank variable). Statistical analysis, comparing corresponding variables between both groups and between particular phases of the study, was performed.

RESULTS

Results of the study are presented in Table 1. During the first visit, patients did not report any significant clinical symptoms since the last 3 days before the visit (0.5–1.5 points) and mean NPIF values were 105.6 (min) – 112.1 (max) l/min. No statistically significant differences in clinical symptom scores and mean NPIF values between LCZ and control groups were found ($p>0.05$). During V2 visit, mean PAR clinical symptoms scores were 4.9–6.0 points and were significantly statistically higher than during V1 visit in case of both groups ($p<0.001$). Also NPIF values were significantly lower in both groups ($p<0.01$). When comparing the mean intensity of clinical symptoms and NPIF values between LCZ group and control group, no significant differences in were found ($p>0.05$).

During the last visit (V3), the diminution of PAR clinical symptoms (in comparison to V2 visit) was observed in the group treated with levocetirizine ($p<0.05$), which was not observed in the control group ($p>0.05$). Differences in intensity of PAR symptoms and in NPIF values between both groups were statistically significant ($p<0.001$). NPIF values increased only in LCZ group ($p<0.02$).

Table 1. Changes of studied clinical symptoms of PAR (in points - pts) and nasal peak inspiratory flow (NPIF) values during three visits (V1, V2, V3) in analysed groups of patients: treated with levocetirizine (LCZ) and receiving placebo

		VISIT 1 (V1) Before the pollen seson x ± SD	VISIT 2 (V2) The peak of pollen season x ± SD	VISIT 3 (V3) The peak of pollen season + 4 weeks x ± SD
Nasal congestion (pts)	LCZ	1.5 ± 0.6	6.0 ± 2.7	3.6 ± 2.8
		p>0.05	p>0.05	p<0.02
	PLACEBO	1.4 ± 0.7	5.8 ± 2.5	5.9 ± 2.6
Sneezing (pts)	LCZ	0.5 ± 0.3	5.4 ± 2.5	2.1 ± 2.1
		p>0.05	p>0.05	p<0.001
	PLACEBO	0.6 ± 0.3	5.6 ± 2.8	6.7 ± 3.0

Rhinorrhea (pts)	LCZ	0.8 ± 0.5	5.7 ± 2.5	2.7 ± 2.2
		p>0.05	p>0.05	p<0.001
	PLACEBO	0.9 ± 0.5	5.3 ± 2.3	6.4 ± 3.2
Itching of the nose (pts)	LCZ	0.5 ± 0.2	5.1 ± 3.1	2.5 ± 2.4
		p>0.05	p>0.05	p<0.01
	PLACEBO	0.4 ± 0.3	4.9 ± 2.6	5.5 ± 2.7
Cumulatively (pts ± SD)	LCZ	0.8 ± 0.4	5.5 ± 1.9	2.7 ± 1.9
		p>0.05	p>0.05	p<0.001
	PLACEBO	0.8 ± 0.5	5.4 ± 1.8	6.1 ± 2.8
NPIF (l/min)	LCZ	112.1 ± 55.0	72.5 ± 32.1	108.0 ± 40.3
		p>0.05	p>0.05	p<0.02
	PLACEBO	105.6 ± 51.4	67.9 ± 37.5	73.0 ± 39.7

DISCUSSION

Although rhinitis (and conjunctivitis) symptoms are not life-threatening, they affect negatively the physical, psychological and social aspects of life and they decrease its quality (3). Modern II generation antihistaminic drugs (levocetirizine, fexofenadine, deslorotadine, norastemizol and others), together with older representants of this group (cetirizine, loratadine, misolastine) are the first-choice treatment in managing and controlling PAR symptoms. They are at least as efficient as their antecedents and they are significantly safer (14, 24, 25). They control all PAR symptoms, except smell disorders (4, 24). When used in allergic rhinitis, they reduce evidently rhinorrhea, itching of the nose and sneezing, although their influence on nasal patency in less evident. Currently, this group of drugs is recommended in all clinical types of PAR (3, 10, 20).

LCZ is a very strong selective antagonist of H1 receptors. It is an R enantiomer of cetirizine, which means – its dextrogyrous form. This drug is characterized by very good pharmacokinetic parameters. It is absorbed rapidly in gastrointestinal tract, reaching after 30–60 minutes its maximal blood concentration. Elimination half-life of LCZ is 8 hours. It is bound by plasma proteins and do not undergo considerable hepatic metabolism. LCZ is a competitive H1 receptor antagonist thanks to which its affinity to these receptors is twice as high as affinity of cetirizine (4, 10, 11). Moreover, it has a significant "extra-receptoral" activity (anti-allergic and anti-inflammatory) (15, 18). It has been proved that LCZ inhibits eosinophils chemotaxis, influences inflammatory response of neutrophiles (inhibition of LTB4 and IL8 production), blocks VCAM1 expression and, via its influence on blood albumin concentration, it changes also vessel permeability (1, 5, 12, 17).

Several studies on LCZ effectiveness in allergic rhinitis treatment have been performed so far. It has been found that levocetirizine is effective in different doses (2.5, 5.0 and 10 mg). Clinical amelioration is observed after only 24 hours of treatment and, what is very important, levocetirizine therapy has been proved to be safe for patients (in relation to placebo and cetirizine) (15, 27). The above results were obtained in conditions of natural exposure to pollen allergens, as well as in controlled exposure studies (6, 25, 26). According to attainable data, such studies have not been performed in Poland yet. The results of our study confirm very high effectiveness of LCZ therapy, in comparison to placebo, in allergic rhinitis treatment of adults sensitized to grass pollen. LCZ remarkably decreased

intensity of clinical symptoms of PAR, even in the peak of grass pollen season (May/June in Lublin). Special attention should be paid to the fact of significant amelioration of nasal patency, which was observed in our study. Decrease of nasal obstruction felt by patients (subjective evaluation in point scale), as well as considerable amelioration of nasal patency in objective test – NPIF – were found. Similar results were obtained in the similar group of patients by Ciprandi et al. (5). Basing on above data, the following conclusions have been drawn:

1. Levocetirizine, taken ones daily in 5 mg dose, is an efficient drug controlling all clinical symptoms of seasonal allergic rhinitis.
2. It is the most effective in fighting such symptoms, as: sneezing, rhinorrhea and itching of the nose.
3. 4-week levocetirizine therapy increases significantly nasal peak inspiratory flow.

REFERENCES

1. Arnold R et al.: Levocetirizine modulates inflammatory response of human neutrophils in the presence of the respiratory syncytial virus. Allergy, 57, (suppl. 73), 146A, 2002..
2. Benedetti M. S. et al.: Absorption, distribution, metabolism and excretion of (14C) levocetirizine, the R enantiomer of cetirizine, in healthy volunteers. Eur. J. Clin. Pharmacol., 57, 571, 2001.
3. Bousquet J. et al.: Allergic rhinitis and its impact on asthma. J. Allergy Clin. Immunol., 108 (suppl.), 147, 2001.
4. Cauwenberge P. et al.: Consensus statement on the treatment of allergic rhinitis. Allergy, 55, 116, 2000.
5. Ciprandi G. et al.: Levocetirizine improves nasal obstruction and modulates cytokine profile in patients with seasonal allergic rhinitis: a pilot study. Clin. Exp. Allergy, 34, 958, 2004.
6. Day J. H. et al.: Comparative clinical efficacy, onset and duration of action of levocetirizine and desloratadine for symptoms of seasonal allergic rhinitis in subjects evaluated in the Environmental Exposure Unit (EEU). Int. J. Clin. Pract., 58, 109, 2004.
7. Durham S. R. et al.: Long-term clinical efficacy of grass pollen immunotherapy. NEJM, 341, 468, 1999.
8. Emeryk A.: Obiektywne badanie drożności nosa w praktyce alergologicznej u dzieci. Alergia, 3, 29, 2003.
9. Eng P. A. et al.: Long-term efficacy of preseasonal grass pollen immunotherapy in children. Allergy, 57, 306, 2002.
10. Górski P. et al.: Leki przeciwhistaminowe. Zastosowanie w praktyce medycznej. Stanowisko Grupy Ekspertów Polskiego Towarzystwa Alergologicznego. The UCB Institute of Allergy, Belgium, 61, 2003.
11. Grzelewska-Rzymowska I.: Leki przeciwhistaminowe drugiej generacji w chorobach alergicznych. Biblioteka Alergologa, t. 3, Biblioteka Łódź, 2001.
12. Jazrawi E. et al.: Effects of levocetirizine in an *in vitro* model of eosinophil chemotaxin induced by eotaxin. Allergy, 56, (suppl. 68), 138A, 2001.
13. Johansson S. G. O. et al.: A revised nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force. Allergy, 56, 813, 2001.
14. Kruszewski J.: Safety of new antihistamines. Pol. Mer. Lek., 14, 648, 2003.
15. Leynadier F. et al.: Efficacy and safety of levocetirizine in seasonal allergic rhinitis. Acta Otorhinolaryngol. Belg., 55, 305, 2001.

16. Lund V. J. et al.: International Consensus Report on the Diagnosis and Management of Rhinitis. Allergy, 49, 1, 1999.
17. Michel L. et al.: Pharmacological study of levocetirizine in independent hypersensivity cutaneous reaction in grass pollen allergy volunteers: demonstration of mediator release and eosinophil recruitment modulation by levocetirizine. Allergy, 56 (suppl. 68), 150A, 2001.
18. Molimard M., Demarteau N.: Comfortable days gained with levocetirizine in patients with perennial allergic rhinitis. Allergy, 57 (suppl.73), 235A, 2002.
19. Passalacqua G. et al.: Long -lasting clinical efficacy of allergen specific immunotherapy. Allergy, 57, 275, 2002.
20. Rapiejko P.: Leczenie alergicznych nieżytów nosa. Terapia, 4, 24, 2004.
21. Rapiejko P. et al.: Progowe stężenie pyłku traw niezbędne do wywołania objawów uczuleniowych. Alergia, 2, 60, 2003.
22. Samoliński B., Śliwińska-Kowalska M.: Alergiczne i niealergiczne nieżyty nosa. Mediton, Łódź 2003.
23. Samoliński B. et al.: Eliminacja i ograniczenie natężenia na alergeny wziewne. W: Standardy w alergologii- część I. UCB Belgium, 59, 2003.
24. Schultz A. et al.: Novel approaches in the treatment of allergic rhinitis. Curr. Opin. Allergy Clin. Immunol., 3, 21, 2003.
25. Stubner P. et al.: A direct comparison of the efficacy of antihistamines in SAR and PAR, randomised, placebo-controlled studies with levocetirizine and loratadyne using an environmental exposure unit – the Vienna Challenge Chamber (VCC). Curr. Med. Res. Opin., 20, 891, 2004.
26. Wang D. T. et al.: Effect of cetirizine, levocetirizine and dextrocetirizine on histamine-induced nasal response in healthy adult volunteers. Allergy, 56, 339, 2001.
27. Xyzal Monograph. UCB Farchim, Switzerland 2002.

SUMMARY

The aim of the study was to evaluate the effectiveness of levocetirizine (LCZ) therapy in patients treated because of pollen allergic rhinitis (PAR). A randomized study, controlled with placebo, was performed. 35 patients were qualified to this study (average age – 25.5 years). 5 mg of levocetirizine in one morning dose, or placebo, were administered to patients during 4 weeks of grass pollen season. Effectiveness of the treatment was evaluated during three visits, basing on the analysis of intensity of PAR clinical symptoms noted in a visual-analogue scale by patients and on nasal peak inspiratory flow measurements. LCZ proved to be an efficient drug, controlling all clinical symptoms of PAR and considerably ameliorating nasal peak inspiratory flow values during grass pollen season.

Wpływ lewocetyryzyny na przebieg pyłkowego alergicznego nieżytu nosa

Celem pracy była ocena skuteczności lewocetyryzyny (LCZ) u pacjentów leczonych z powodu pyłkowego alergicznego nieżytu nosa (ANNp). Przeprowadzono randomizowane badanie, kontrolowane placebo, do którego zakwalifikowano 35 chorych (średnia wieku 25,5 lat). Zastosowano 5 mg LCZ w jednorazowej dawce porannej przez 4 tygodnie w czasie trwania sezonu pylenia lub placebo. Skuteczność leczenia oceniano w oparciu o analizę intensywności objawów klinicznych ANNp, notowanych w skali wizualno-analogowej przez pacjenta oraz pomiarów nosowego szczytowego przepływu wdechowego podczas trzech wizyt. LCZ okazała się lekiem skutecznie kontrolującym wszystkie objawy kliniczne ANNp oraz poprawiającym istotnie nosowy szczytowy przepływ wdechowy w trakcie sezonu pylenia traw.