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Role and place of antihistamines in the treatment of allergic rhinitis. Assessment of the therapeutic effect of Glentset according to results of a multicenter study

Key words: Allergic rhinitis, histamine, levocetirizine, Glencet, rhinorrhea, itchy nose, watery eyes, coughing, nasal congestion.

Today allergy is a public health problem of pandemic proportions, from which only in Europe suffers more than 150 million people. Taking into account the epidemiological trends, European Academy of Allergy and Clinical Immunology (EAACI) foresees that in less than 15 years more than half of Europe's population will suffer from one or another kind of allergy.

Allergic rhinitis (AR) – is a disease caused by allergens and characterized by IgE-dependent inflammation of the nasal mucosa. It is manifested by the classic triad of symptoms: rhinorrhea, sneezing, nasal breathing violations (including smelling).

Until 2001, it was decided to classify the AR two main forms: seasonal (SAR), which is mediated by the sensitization to pollen allergens and perennial (PAR), associated with a reaction to household allergens. In 2001, this classification was revised by the experts of the World Health Organization. The new version takes into account the symptoms and quality of life of the patient. According to it AR can be intermittent and persistent based on the duration of symptoms.

Data from epidemiological studies conducted in many countries have shown that 10 to 25 % of the general population suffers from AR [1, 8], and the prevalence of seasonal allergic rhinitis (SAR) ranges from 1 to 40%, perennial (PAR) from 1 to 18 % [2, 9]. за последние два десятилетия The incidence of AR has increased in all countries is 3 to 4-fold over the past two decades, including Ukraine. The prevalence of SAR in the world ranges from 7 to 22 %. In Ukraine (according to calculated data) SAR prevalence ranges from 3 to 8 %. In children, depending on the age, the frequency of

the disease is 0 to 5 %. Now it is possible to detect SAR in preschoolers, although in the past it was typical only for older children and adolescents [2, 5]. Despite that the developing rhinitis symptoms are not life threatening, they create significant discomfort, dramatically reduce performance, greatly reduce the quality of patient's life. Taking into account that structure and functioning of the mucosa of the upper and lower respiratory tract are similar, delayed treatment of various forms of rhinitis can lead to the development of asthma symptoms. It is well known that 20 to 38 % AR patients have asthma, at the same time 60 to 78 % asthma patients experience rhinitis symptoms [3, 8].

By the example of AR we can see what is happening in the body tissues. So-called mast cells located under the nasal mucosa play the main role in this process. Increased production of specific substances (antibodies) is observed in individuals with a genetic predisposition while exposed to the allergen. Antigens and antibodies are fixed to mast cell containing to 500 histamine granules. Cell is activated and histamine is released, which, being a biologically active substance, causes vasodilatation, increased permeability of the microvasculature vessels and edema development with the release of large amounts of fluid to the external environment. There is also a hypersecretion of mucus glands that are located in the nasal cavity. Pollen, mold spores, animal dander, and house dust can cause allergy. Therefore, it is necessary to take measures to remove allergens from the environment; at the same time the majority of patients have a need in medical treatment, in which antihistamines are widely used [3, 5, 8].

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Histamine was synthesized in 1907. In 1909, it was extracted from ergot. A series of studies carried out in the 20 years of the twentieth century, made it possible to establish that histamine is an important mediator of allergic reactions such as anaphylaxis, rhinitis, asthma, urticaria. There are H_1 , H_2 and H_3 histamine receptors in the human body [4, 7, 9].

The study of antihistamines was initiated in the late 1930s, and in 10 years they have been used to treat various diseases. H_1 blockers are drugs that are traditionally used in allergic diseases. Currently there are more than 150 antagonists of H_1 histamine receptors formulations. They remove the itchy nose, sneezing and rhinorrhea symptoms, but do not affect the nasal obstruction during exacerbation of AR. Since the late 1970s the introduction of 2nd generation antihistamines into wide medical practice began. Their high selectivity in H_1 receptor blockade and the lack of interaction with other receptors should be noted. Anti-allergic action starts in 20 minutes and stays quite a long time – up to 24 hours. These medications are available only in tablet form. They are given once or twice daily. It is preferable to 1st generation of histamine antagonists that are usually used three times a day. 2nd generation histamine antagonists are not addictive, and cause no sedation. 2nd generation formulations have no anti-cholinergic effect and do not cause dryness of mucous membranes, can be used to treat AR accompanied with asthma, where previously antihistamines were contraindicated because of the worsening of expectoration that they caused [7, 9].

E. Baltes while studying the properties of hydroxyzine found that its antihistamine effect is much longer than the sedative one, and suggested that it is not hydroxyzine that has the antihistamine action but one of its metabolites. Only in 1978 it was able to decipher the molecule of cetirizine, isolate and synthesize it. Cetirizine was the first of antihistamines – natural metabolites.

For many years it was known that cetirizine is a racemic mixture of two isomers, levocetirizine and dextrocetirizine. It was also known that H_1 histamine receptor is a stereoselective structure, and preferably binds only one of the isomers [9]. Only in 2001 it became possible to apply the technology, allowing successfully split the enantiomers of cetirizine. Levocetirizine is the first example of the release of the active enantiomer of the human metabolite as an independent anti-allergic formulation [5, 9].

Levocetirizine has 2-fold greater affinity for the H_1 receptor than cetirizine. It has 100 % bioavailability. Its effect starts after 12 minutes after receiving a single dose, and persists 24 hours. A good safety profile, lack of sedation and no effects on psychomotor functions substantiate levocetirizine to be prescribed to people engaged in activities that require attention. It should be noted that levocetirizine is used in SAR for quick relief of symptoms, because its action starts after 12–20 minutes after taking the pill. Levocetirizine is also used as a basic therapy for PAR, along with other long-acting medications [2, 7, 9].

Currently, AP pharmacotherapy is based on medicines that target major pathogenetic mechanisms of allergic inflammation [6]. Most widely used among them in today's clinical practice are H_1 receptor antagonists that are able to block the effects of histamine by competitive binding of its receptors. A

new generation medications in this group don't only block receptors, but also suppress the production of histamine and other mediators of the allergic late phase response, and that is what their anti-inflammatory effect based on. These and other pharmacokinetic advantages of modern antihistamines (high affinity for the H_1 receptor, rapid and prolonged action, lack of tachyphylaxis, a high safety profile) are the underlying cause of their preference in AR patients [7, 8].

Currently, there is a medication Glentset on Ukrainian market (firm «Glenmark») containing levocetirizine dihydrochloride 5 mg in pills.

An open, multicenter, parallel-group study, which involved 11 regions of Ukraine – Odessa, Donetsk, Lugansk, Crimea, Kiev, Kharkov, Dnepropetrovsk, Zaporozhye, Lvov, Lutsk, Khmelnytsky, was held.

The aim of this study was to investigate the therapeutic efficacy of antihistamine Glentset in patients with persistent and intermittent AR.

Criteria for inclusion: patient of 18 years age and older; confirmed by either a positive skin prick test or a positive serological test to the relevant allergenic allergen AR disease of at least 2 years duration; AR clinical symptoms at baseline – patients with a minimum final grade of nasal symptoms (nasal congestion, itching, and sneezing) ≥ 6 , and rhinorrhea ≥ 2 (moderate); willingness to adhere to medication dosage and schedule visits.

Exclusion criteria: pulmonary diseases, sinusitis, drug-induced rhinitis, pregnancy or breast-feeding.

All patients received a standard dose of Glentset (1 pill) in the morning before or during a meal followed by evaluation of symptoms and signs. In addition, it was pointed time of onset of effect, as well as its duration. Analysis of the Glentset efficacy was conducted by comparative assessment in the doctor-patient points to intermittent and persistent course of AR: 3 points – an excellent result, 2 – good, 1 – satisfactory, and 0 – no effect. The survey results were put into a specially designed card and then analyzed.

Results of the study

In total 2584 patients were treated, of which 1150 (44.50%) with intermittent (seasonal) AR, and 1434 (55.50%) persistent (perennial) AR. There were 1128 (43, 65%) men and 1456 (56.35%) women of 18 to 72 years age (mean age was 31.8 ± 1.7).

Patients expressed the following complaints (*Figure 1*):

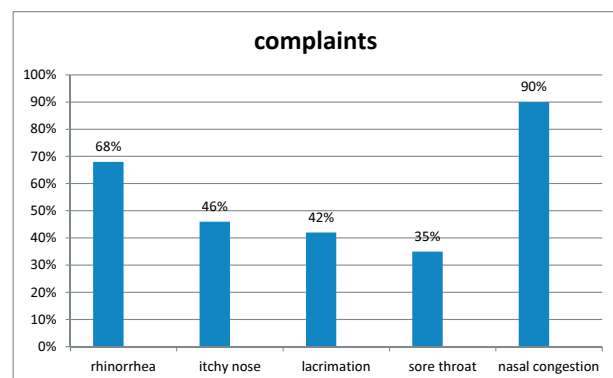


Figure 1. The frequency and nature of patients' complaints

- nasal congestion – 2325 (89,97 %);
- rhinorrhea – 1757 (67,99 %);
- itchy nose – 1188 (45,97 %);
- lacrimation – 1135 (43,92 %);
- sore throat and cough – 904 (34,98 %).

Thus, in 97.91 % of the observed patients a therapeutic effect developed within 60 minutes, indicating the high efficacy of Glentset. Commonly the clinical effect was observed in 15–30 minutes (*Figure 2*).

An effect duration of more than 24 hours is one of the requirements for modern antihistamines. This allows one to take the drug once a day. Therefore, the study drew attention to the absence of symptoms of AR in a day after taking a pill of Glentset. It was noted that in 75 % of patients at the end of the day the symptoms of AR were diminished to the level of 2–3 points. In 13% persons a little therapeutic effect was observed, and 12 % of the patients had uncontrolled allergy symptoms within 24 hours after receiving Glentset (*Figure 3*)

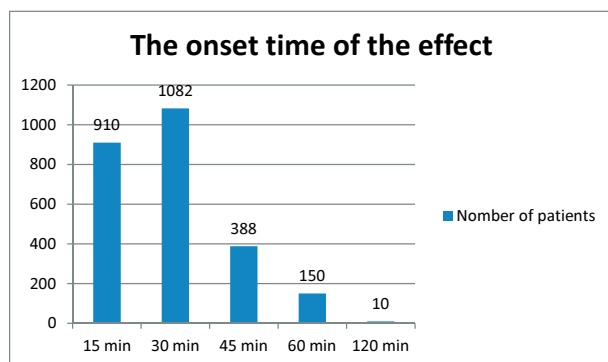


Figure 2. The onset time of the effect

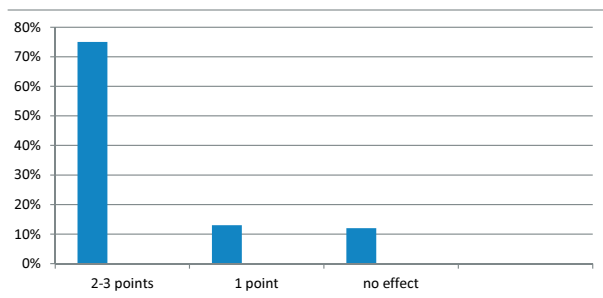


Figure 3. Glentset efficacy in 24 hours

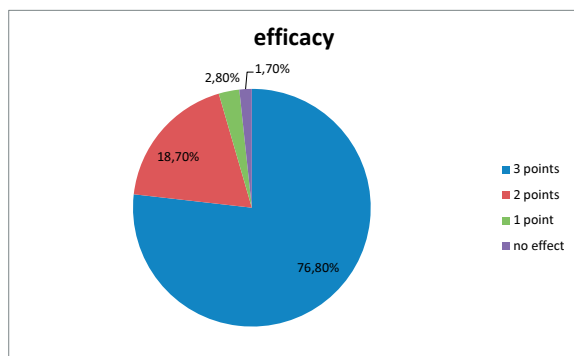


Figure 4. The efficacy of Glentset

Effect of Glentset in relieving symptoms of AR was 98.25%. Only 1.75% of patients (44 people) observed no effect during the treatment. The data on *Figure 4* are the subjective evaluation of Glentset efficacy:

- 3 points 1984 patients (76,78 %);
- 2 points 483 patients (18,69 %);
- 1 point 73 patients (2,82 %).

As it is shown on *Figure 5*, Glentset effectively acted on all the symptoms of rhinitis, especially on rhinorrhea, itchy nose and sore throat.

Improvement of nasal breathing while taking the Glentset begins after 4–5 minutes and reaches its maximum after 2 hours, in some patients in 10 hours (*Figure 6*). Thus, improving nasal breathing while taking Glentset was not achieved in all patients, that is a commonly for antihistamines.

Myxopoiesis is a leading symptom of allergic AR, caused predominantly by stimulation of histamine receptors. Therefore it is clear that all of our patients reported high clinical effect in the form of reduction of rhinorrhea (*Figure 7*), which is observed in 45–60 minutes in almost all patients.

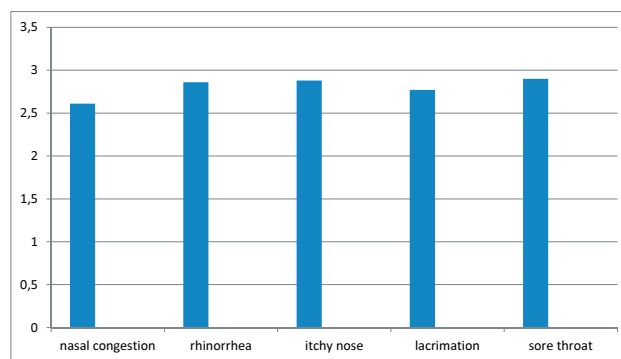


Figure 5. Reduction of symptoms during the day

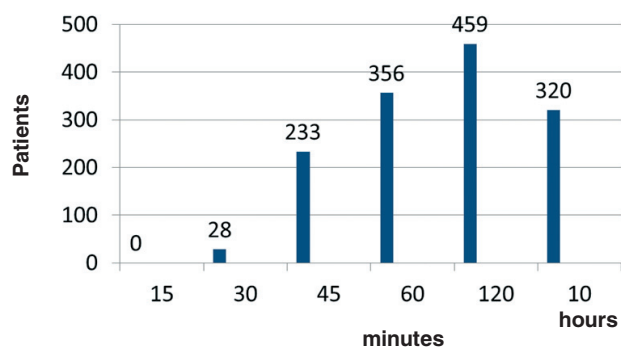


Figure 6. Improvement of nasal breathing

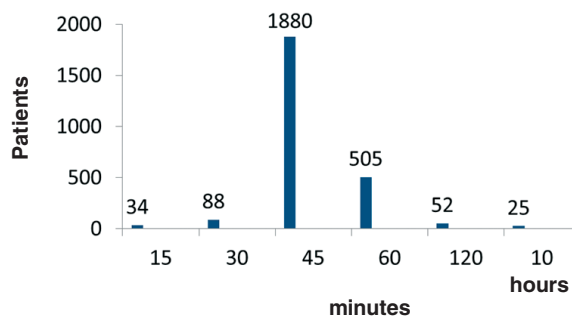


Figure 7. Reduction of rhinorrhea

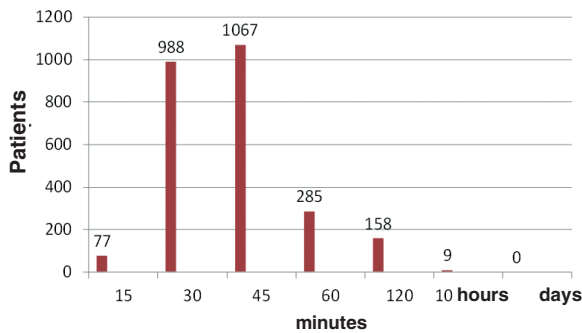


Figure 8. Reduction of the nasal itching

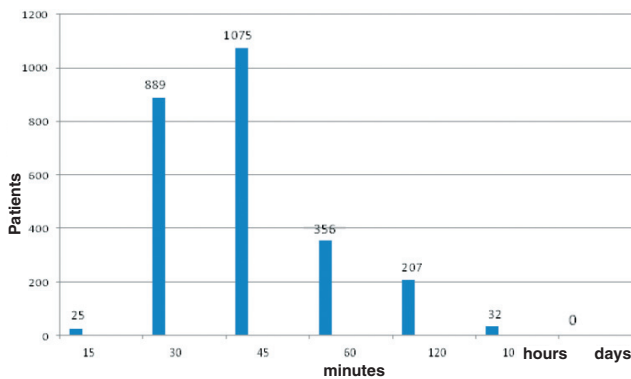


Figure 9. Reduction of lacrimation

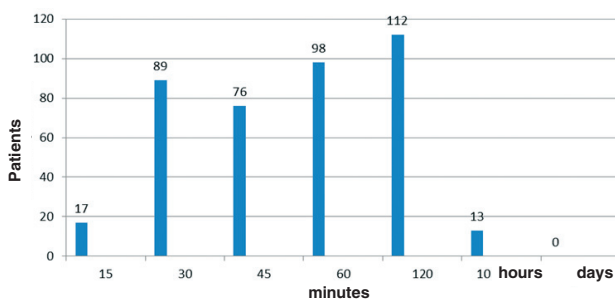


Figure 10. Cough reduction

The best results while taking Glentset reflected in irritation symptoms reduction – itchy nose (Figure 8) was significantly reduced and disappeared completely within 30–45 minutes. The same results were observed when assessing the lacrimation (Figure 9)

Least significant results of antihistamines are detected in the evaluation of cough symptoms, as leukotrienes are considered to have a leading role in the development of this symptom. Our studies (Figure 10) also confirmed these findings – only 15,67 % of patients (405 persons) reported cough reduction. Moreover, this symptom was reducing during longer periods of time – from 30 minutes to 2 hours.

Safety of this medication should be noted – the vast majority of patients did not report any adverse events. Only 76 (2.94%) people pay attention to mild adverse effects that disappeared after withdrawal of Glentset and did not require taking other medications. The following side effects were observed: drowsiness – 23 (0.89%) patients, dry mouth – 34 (1.31%), headache – 18 (0.69%), pain in the right upper quadrant of abdomen – 1 (0.04%).

Conclusions

Modern antihistamines are highly effective symptomatic agents for the treatment of various forms of AR.

Glentset containing 5 mg of levocetirizine is:

- highly active formulation – its therapeutic activity was observed in 98.3% of patients;
- fast-acting medication – its effect is obtained in 98.3% of patients within 60 minutes after administration;
- long-acting formulation – its effect lasts for 24 hours, allowing to take it once a day;
- safe medication – 97,06 % patients did not report any adverse events and adverse effects that occurred in individuals were mild and did not require additional intake of medicines.

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РОЛЬ ТА МІСЦЕ АНТИГІСТАМІННИХ ПРЕПАРАТІВ У ЛІКУВАННІ АЛЕРГІЧНОГО РИНИТУ. ОЦІНКА ТЕРАПЕВТИЧНОГО ЕФЕКТУ ПРЕПАРАТУ ГЛЕНЦЕТ ЗА РЕЗУЛЬТАТАМИ БАГАТОЦЕНТРОВОГО ДОСЛІДЖЕННЯ

С. М. Пухлик, І. В. Дедікова та ін.

Резюме: Поширеність алергічного риніту (АР) становить 10 – 25 % населення в загальній популяції. За останні два десятиліття захворюваність АР зросла у всіх країнах у 3 – 4 рази, в тому числі і в Україні. Незважаючи на те, що симптоми, які розвиваються при риніті (ринорея, свербіж у носі, слезотеча, закладеність носа) не є загрозливими для життя, вони створюють значний дискомфорт, різко знижують працездатність, помітно знижують якість життя пацієнта. Гістамін є найважливішим посередником таких алергічних проявів, як анафілактичний шок, риніти, бронхіальна астма, кропив'янка. H1-блокатори – препарати, що традиційно застосовуються при алергічних захворюваннях. Основу фармакотерапії АР на даний час складають лікарські засоби, дія яких спрямована на основні патогенетичні механізми алергічного запалення. Левоцетиризин є першим прикладом виділення активного енантіомеру людського метаболіту як самостійного протиалергічного препарату. В даний час на українському ринку з'явився препарат Гленцет (компанія «Гленмарк»), що містить левоцетиризину дигідрохлориду 5 мг у формі таблеток. Проводилось відкрите багатоцентрове паралельне дослідження, в якому брали участь 11 областей України – Одеса, Донецьк, Луганськ, Крим, Київ, Харків,

Дніпропетровськ, Запоріжжя, Львів, Луцьк, Хмельницький. Всі хворі приймали Гленцет в стандартному дозуванні – по 1 таблетці вранці до або під час їжі з подальшою оцінкою динаміки симптомів АР. Крім цього, зазначалися час настання ефекту і його тривалість. Аналіз ефективності препарату Гленцет проводився за допомогою порівняльної оцінки лікарем і хворим в балах. Результати обстеження заносилися в спеціально розроблену карту, по якій потім проводили аналіз результатів дослідження. За результатами дослідження препарат Гленцет показав високу терапевтичну активність, швидке настання ефекту, тривалу дію і був безпечним.

Ключові слова: Алергічний риніт, гістамін, левоцетиризин, Гленцет, ринорея, свербіж у носі, слезотеча, кашель, закладеність носа.

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**THE ROLE AND PLACE OF ANTIHISTAMINE DRUGS
IN THE MANAGEMENT OF ALLERGIC RHINITIS.
THE EVALUATION OF GLEN CET EFFICACY BASED
ON THE RESULTS OF MULTICENTRE STUDY**

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Summary: The prevalence of allergic rhinitis (AR) is 10 – 25 % in the general population. Over the past two decades, the incidence of AR has increased 3- to 4-fold in all countries, including in Ukraine. Despite the fact that developing rhinitis symptoms (rhinorrhea, nasal itching, watery

eyes, nasal congestion) are not life threatening, they create a significant discomfort, dramatically reduce capacity for work, noticeably reduce the quality of human life. Histamine is an important mediator of allergic reactions such as anaphylaxis, rhinitis, asthma, urticaria. H1-blockers are the drugs that are traditionally used in allergic diseases. The pharmacotherapy of AR is currently based on drugs that target major pathogenetic mechanisms of allergic inflammation. Levocetirizine is the first example of the active human metabolite enantiomer extraction as an independent anti-allergic drug. Currently Glencet (company "Glenmark") containing levocetirizine dihydrochloride 5 mg in tablets has appeared on the Ukrainian market. The open-labeled, multicenter, parallel-group study involving 11 regions of Ukraine – Odessa, Donetsk, Lugansk, Crimea, Kiev, Kharkov, Dnepropetrovsk, Zaporozhye, Lvov, Lutsk and Khmelnytsky was held. All patients received a standard dose of Glencet – 1 tablet in the morning before or during a meal, followed by assessment symptoms dynamics. In addition, it was pointed time of effect onset, as well as its duration. Analysis of the Glencet effectiveness was conducted by the doctor's and patient's comparative assessment of the drug in points. The survey results were put into a specially designed card on which then the results of the study were analyzed. In this study high therapeutic activity, rapid onset of action and long-term effect of Glencet were showed.

Key words: Allergic rhinitis, histamine, levocetirizine, Glencet, rhinorrhea, itchy nose, watery eyes, coughing, nasal congestion.

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