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# Clinical and functional efficiency of combined drug momethason fuorat / azelastin in patients with allergic rhinitis

**Key words:** *allergic rhinitis, azelastine hydrochloride, mometasone furoate, rhinomanometry, technology of patient selection.*

Over the past decade, there has been a steady increase in allergic diseases worldwide, which has now reached a high level and remains one of the most important unsolved medical and social problems for the coming years. According to the WAO, in 2013, 20-40% of the population of different countries are diagnosed with one or more allergic diseases (AD). A significant proportion of patients are children and adolescents [12]. Increasingly occurs multiple sensibilisation, allergic manifestations acquire a multi-organ character. Such a high incidence increases the burden on health services, leading to high socio-economic costs. To date, the costs of treating allergies in Europe are estimated at about 100 billion euros per year [5].

The current situation has disappointing forecasts. According to the research of scientists from different countries, the scale of allergic pathology can expand even more as a result of deterioration in environmental conditions, increasing industrial air pollution, as well as climate change – the effects of global warming.

These changes in the environment will affect on content of pollen and other allergens, the population of stinging insects and molds that cause allergies. Prophylaxis of AD in many countries is variable and fragmentary, which leads to a decrease in the quality of life of patients, increasing morbidity and mortality [12]. At the same time, clinical manifestations of allergy become more severe, and the incidence of anaphylaxis has increased by 7 times today. Allergic rhinitis (AR) occupies a leading place among allergic diseases and is one of the topical problems of modern medicine, which is due to their wide distribution, the influence on the occurrence and course of bronchial asthma, frequent exacerbations and a tendency to complications (such as: sinusitis, polyposis etmoiditis, tubootitis, acute and chronic otitis media).

Consequently, to engage in this problem and be a master in methods of diagnosis and treatment of AR is necessary for doctors of various specialties – otolaryngologists, pulmonologists, allergologists and general practitioners. Lack of continuity in the examination of patients by physicians of these specialties often leads to late diagnosis of AR and bronchial asthma (BA) [5]. Data on the incidence of AR, based on the patient's visits, do not reflect the true prevalence of this pathology, they do not take into account a huge number of people who have not applied for medical care, and patients who have not been correctly diagnosed by the physician at the primary care stage.

Over the last century, the prevalence of AR has grown tens of times. Epidemiological studies in the population indicate that in developed countries AR affects from 10% to 30% of the population. The peak of the disease occurs in the age range from 15 to 44 years. In 80% of patients, symptoms of AR occur before the age of 25 years. But at the same time the incidence of AR among elderly patients continues to increase [5].

Thus, AR are in the population of 3–20%, depending on the region of the study. In some professional groups this indicator can reach 25%. And in patients with bronchial asthma, AR is diagnosed in 66–95% of cases [4].

Clinically AR also be in great changes. In addition, often this pathology occurs against the background of other AD, there is a worsening of the course of symptoms of AD. At the same time mixed forms of rhinitis began

to prevail. Many patients experience polysensibilisation. Increased appearance of AR phenotypes resistant to drug therapy, which often leads to an uncontrolled course of the disease. In addition, AR has a negative impact on all aspects of the patient's life – sleeping, work, education, physical activity, emotional state [5, 16].

Therefore, the goal of treating this pathology is to achieve control over the course of the disease and normalize the quality of life of patients

Interview of patients showed, that most of them use several drugs to control the symptoms of AR, in order to achieve a more rapid and complete elimination of the symptoms of the disease. In this case, patients note that the use of 1 drug in place of 2 is more convenient to use and increases patient adherence to treatment [5]. All of the above was an impetus for researchers to search for new combination drugs that would combine the effects of several and increase the effectiveness of treatment of this category of patients [7, 11].

Inhalatory glucocorticosteroids (ICS) in the form of nasal aerosols are by far the most effective method of AR treatment. Regular use of ICS has a pronounced effect on all symptoms of the disease. A number of placebo-controlled clinical trials have confirmed the high efficacy of ICS: mometasone furoate, fluticasone propionate, budesonide, beclomethasone dipropionate. With AR, they are more effective than systemic and topical antihistamines, as well as sodium cromoglicate [10].

Low bioavailability of modern ICS is due to their minimal (0,1-8%) absorption from the gastrointestinal tract and almost complete (about 100%) biotransformation to inactive metabolites at the first passage through the liver. The small part of the drug, which is absorbed from the mucous membrane of the respiratory tract, is also hydrolyzed by esterases to inactive substances. These features of the pharmacokinetics of ICS allow long-term use of the necessary dose of the drug without the risk of developing systemic side effects.

In recent years, the development of new intranasal GCS has been focused on the creation of effective drugs with high anti-inflammatory activity, minimal systemic and local side effects and rapid development of the clinical effect. The result of this work was the creation of the mometasone furoate, released in the form of a dosed aqueous aerosol. The drug has a pronounced anti-inflammatory and anti-allergic effect due to the high affinity of mometasone to glucocorticosteroid receptors (several times higher than other intranasal steroids), inhibitory action against proinflammatory cytokines and metabolic products of arachidonic acid (cyclic endoperoxides and prostaglandins). As a consequence, mometasone inhibits the migration of macrophages and neutrophils, which contributes to a reduction in the processes of inflammatory exudation, infiltration and granulation, and thus influences both the early and the late phases of the allergic response [17].

In vitro studies, it was shown that the drug inhibits the synthesis and release of histamine, leukotrienes, interleukins (IL1, IL4, IL5, IL6, IL8), α-interferon and tumor necrosis factor of the first and second order target-cells. In patients with seasonal AR who received mometasone furoate in a daily dose of 200 μg, the histamine content in the nasal secretion after provocation by the allergen was significantly lower in comparison with patients receiving placebo. The action of mometasone furoate on the late phase of the allergic reaction is confirmed by a decrease in the content of IL6, IL8, ICAM-1 and eosinophils in the nasal cavity [12].

The highest between intranasal GCS final viscosity of mometasone furoate provides a long-term presence of the drug in the pathological focus (it does not flow down the posterior wall of the nasopharynx and does not flow out of the nose). Therefore, taking mometasone furoate once a day allows to monitor all the symptoms of allergic rhinitis, including nasal congestion, within 24 hours. Mometasone furoate does not cause dryness in the nasal cavity, since it includes a moisturizer. After a 12-month treatment with this drug, there is no evidence of atrophy of the nasal mucosa, normalizing the histological pattern in the study of biopsies of the nasal mucosa [17].

Mometasone furoate as well as all ICS is characterized by a relatively slow onset of action, its maximum effect develops within a few days, so it should be applied regularly. In severe forms of seasonal allergic rhinitis, treatment should be started 2 weeks before the beginning of the flowering season. Many patients, in order to achieve a more rapid effect in parallel with the endonasal ICS, take decongestants, which can affect of the nasal mucosa. To avoid such negative influences, a drug was developed that is a fixed combination of azelastine hydrochloride 140 μg + mometasone furoate 50 μg. The choice of this combination is due to the fact that azelastine has a unique pharmacological effect, which is much broader than the action of antihistamines. It not only is an antagonist of H1-histamine receptors, but also regulates the transport of calcium ions reduces the release and inflow of Ca2+ into the cell, reduces the amount of leukotrienes and oxygen free radicals, reduces the number of cellular adhesion molecules (ICAM-1) and eosinophils, decreases level of IL-4 and CD23, which causes triple mechanism of action of this drug – azelastine exhibits antihistaminic effect as oral antihistamines, mast cell membrane stabilizing like cromones has antiinflammatory action as a nasal steroids. In addition, with its endonasal administration, the relief of symptoms of AR is noted from 15 minutes after application and lasts up to 12 hours or more. There are no side effects that are observed with the use of decongestantes [1, 6, 8, 13, 14].

In the medical literature to date, published 256 studies and scientific works proving the high efficacy and safety of mometasone furoate – intranasal spray and 207 studies and scientific works proving the high effectiveness and safety of azelastine – intranasal spray.

However, in literary there is no objective data on the tactics of selecting patients for treatment with a combined drug azelastine hydrochloride 140 μg + mometasone furoate 50 μg and its clinical and functional efficacy in this selection of patients.

***The aim*** – to investigate the clinical and functional efficacy and tolerability of the combined drug mometasone furoate

50 μg/azelastine hydrochloride 140 μg, 1 puff in each nostril BID, during 30 days in patients with moderate / severe allergic rhinitis (AR).

***Object of study.*** The study involved twelve patients with a whole year moderate/severe persistent AR, ≥ 18 years of age.

This work was financed from the state budget of Ukraine.

**Materials and methods**

In the course of the examination of the patients, the following was done: the collection of an anamnesis with the determination of the age at which the patient was diagnosed with AR, the duration of the disease, the treatment that the patient received, the identification of adherence to treatment, the attitude to smoking, the presence of concomitant pathology (according to the patient and the availability of extracts). The obtained data were recorded in an individual patient card.

To control the four main symptoms of AR (rhinorrhea, nasal congestion, itching in the nose, sneezing) before and during the treatment, a conventional ball system was used - the scale TNSS (Totel nasal symptom score). For this system, the symptoms of rhinitis were assessed using a 4-level scale with values from 0 to 3, where 0 is the absence of a symptom; 1 - slightly expressed symptom; 2 - moderate; 3 - severe manifestations of the symptom. Symptoms were evaluated by the patient every day for every 24 hours and the data were recorded in a diary. Then, the mean value of the TNSS scale was calculated. The higher the score, the less controlled the symptoms of AR were in the patient. To obtain a more complete picture of AR treatment, eye symptoms were also taken into account, which are almost always present when the pathology is exacerbated. A general assessment of the severity of eye symptoms TOSS (Totel ocule symptom score) included 3 symptoms: pruritus, redness of the eyes and lachrymation, Which were also assessed using a 4-level scale: 0 - no symptom; 1 - slightly expressed symptom; 2 - moderate; 3 - severe manifestations of the symptom [5, 9].

The endpoint of the study was chosen primary efficiency index - deviation from the baseline TNSS. Symptoms were assessed once a day in the evening on a 4-point scale (0 - 3, daily maximum = 12 points).

Additional efficacy parameters are:

– retrospective general assessment of the severity of eye symptoms - TOSS (itching and redness of eyes, lacrimation, daily maximum = 9)

– retrospective general assessment of the 7 symptoms – T7SS (TNSS plus TOSS; daily maximum T7SS = 21), characterizing the overall rhinoconjunctival symptom-response in AR.

To identify the severity of AR symptoms and assess their impact on quality of life, patients were asked to complete a sino-nsaal score questionnaire SNOT-22 [15] before and after treatment.

When objective examination of ENT organs, the following conventional methods were used: anterior and posterior rhinoscopy, pharyngoscopy and indirect laryngoscopy [2]. Rinomanometry was performed on aparate "Master Screen PFT" SN 675123, 2008 p. Manufactured by «Cardinal Health» (Germany) in application "Rhinoscreen". The following indicators were studied: nasal flow inspiration right (FIR), nasal flow expiration right (FER), nasal flow inspiration left (FIL), nasal flow exspiration left (FEL), resistance inspiration right (RIR), resistance exspiration right (RER), resistance inspiration left (RIL), resistance exspiration left (REL), totas nasal flow on inspiration (FSUMI), totas nasal flow on exspiration (FSUME). The study was carried out according to the methodology of the firm that developed the equipment.

Taking into account, that some patients are resistant to drug therapy, was worked out a technology for selection of patients for treatment with a combination drug. With this aim all patients were underwent rhinomanometry before and after 15 and 60 minutes after 1 puff of study drug (azelastine hydrochloride 140 μg + mometasone furoate 50 μg) into each nostril.

Such time intervals in the test were chosen taking into account the fac,t that azelastine, which is part of the drug, causes a weakening of the symptoms of AR starting from 15 minutes from the moment of it's administration, and after 60 min this effect is enhanced due to the complementary action of both drugs - Azelastine hydrochloride and mometasone furoate. Test was assesessed as positive when total nasal flow on inspiration (FSUMI) and expiration (FSUME) increased more than 20.0%, and on this background study drug was prescribed.

Data collection and mathematical processing carried out by licensing software products included in the package Microsoft Office Professional 2007 license Russian Academic OPEN No Level № 43437596. Statistical analysis was performed using mathematical and statistical features MS Excel, as well as additional statistical functions developed by S.N. Lapach, A.V. Tschubenko, P.N. Babich [3].

**Results and discussion**

After a detailed survey, only 10 of them participated in a further study. One of the retired patients had a positive pregnancy test, and the second had no increase in the total nasal flow in the test with study drug.

The conducted questioning and clinical and functional examination of patients before treatment revealed that all patients exacerbated rhinitis symptoms associated with allergens.

At the same time, only 70% of patients with AR had allergic tests. In all 70% of patients, positive samples were detected for household allergens, 30% for pollen, 10% for food allergens, and 20% for bacterial allergens. Positive samples for several types of allergens were noted in 30% of patients. However, not all 70% of patients with allergic tests in the anamnesis had allergological tests for food and bacterial allergens, which indicated an insufficient survey of patients with AR.

The average duration of AR (since the official diagnosis) was (9.9 ± 2.7) years, although many patients reported the appearance of the first symptoms of AR much earlier.

At the time of the beginning of the examination, all patients noted that, with exacerbation, clinical symptoms

of AR appear and continue to disturb more than 4 days per week or 4 weeks per year, which corresponded to the persistent course of the disease. The severity of nasal clinical symptoms on the TNSS scale was (7.5 ± 0.5) points, eye symptoms on the TOSS scale (4.9 ± 0.8) points, T7SS - (12.4 ± 0.7) points, which corresponded to moderate severity of the disease (table 1).

In all 100% of patients, the severity of AR symptoms led to sleep disturbance, 40% to daytime activity and leisure, 50% to negatively affect work and education, 80% to emotional state, and 50% to privacy.

From the anamnesis it is known that earlier all examinees took endonasal inhalation GCS with a positive efficacy of treatment. 80% of patients used vasoconstrictive drops, another treatment (systemic antihistamines, physiotherapy, sanation of the nasopharynx with saline solutions) was used by 60% of the subjects.

Most patients, except AR, had 1 or 2 other concomitant ENT diseases (table 2). Thus, two of the examined patients were operated on for chronic bilateral polyposis etmoiditis (without relapse in the subsequent period). This complication of AR, as a chronic eustachitis, was observed in one subject. Deviation of the nasal septum and chronic tonsillitis are diagnosed in 30% of patients. Concerning chronic purulent maxilloimitis, 1 patient was observed.

All patients before treatment with a combined preparation rhinomanometry tests were performed (azelastine hydrochloride 140 mcg + mometasone furoate 50 mcg). The drug was used for 1 puff into each nostril. The data of rhinomanometry are presented in table 3.

In all 10 patients who participated in the study, the pharmacological test with the study drug was positive. Already at 15 minutes, 80% of patients had an increase in the total nasal flow by more than 20,0%, and an hour later this increase was more than 50,0%. Note that before the treatment, the total nasal flow on the inspiration was greater than on exhalation, which indicated an increased load on the respiratory musculature during exhalation. The same pattern was observed in the test. At the same time, after 15 minutes, the increase in the total nasal flow during inspiration was practically unchanged (increased only by 8,1%), and the increase in the total nasal flow on exhalation increased by 55,2%, which was 1,5 times higher than the baseline level. After 60 minutes, the increase in the total nasal flow on inspiration increased more than 1,5 times, and on exhalation more than 2,5 times, but the absolute value of the total nasal flow on inspiration FSUMI – (516,8 ± 88,3) ml/s remain higher then in expiration FSUME – (410,8 ± 83,2) ml/s (table 3). After 30 days of treatment, the total nasal flow on inspiration and expiration statistically significantly increased and had approximately the same values FSUMI – (643,6 ± 71,9) ml/s and FSUME – (610,7 ± 109,3) ml/s.

In parallel with the improvement in aerodynamic parameters of the upper respiratory tract, the clinical symptoms of AR. There was a statistically significant improvement in all symptoms of AR on a scale TNSS from (7,5 ± 0,5) score to (1,4 ± 0,4) score, $p < 0,05$. Also, the eye symptoms changed statistically reliably on a scale TOSS – from (7,5 ± 0,5) score to (1,4 ± 0,4) score, $p < 0,05$.

Total score T7SS decreased from (12,4 ± 0,7) score to (1,9 ± 0,4) score, $p < 0,05$ (table 1, fig. 1).

*Table 1*

**Nasal and ophthalmic clinical symptoms in the examined patients before and after treatment with the drug (azelastine hydrochloride 140 mcg + mometasone furoate 50 mcg) (M ± m)**

| Clinical symptoms | Score | |
|---|---|---|
| | Before treatment | After treatment |
| **Scale TNSS (Total nasal symptom score)** | | |
| Rhinorrhea | 2,2 ± 0,1 | 0,7 ± 0,2* |
| Nasal congestion | 2,3 ± 0,2 | 0,5 ± 0,2* |
| Itching in the nose | 1,5 ± 0,2 | 0,1 ± 0,1* |
| Sneezing | 1,6 ± 0,2 | 0,1 ± 0,1* |
| Total score | 7,5 ± 0,5 | 1,4 ± 0,4* |
| **Scale TOSS (Total ocule symptom score)** | | |
| Pruritus | 1,7 ± 0,3 | 0,0 ± 0,0* |
| Redness of the eyes | 1,7 ± 0,3 | 0,3 ± 0,2* |
| Lachrymation | 1,6 ± 0,2 | 0,2 ± 0,1* |
| Total score | 4,9 ± 0,8 | 0,5 ± 0,3* |
| T7SS | 12,4 ± 0,7 | 1,9 ± 0,4* |

Note: * – statistically significant difference between results before and after treatment ($p < 0,05$).

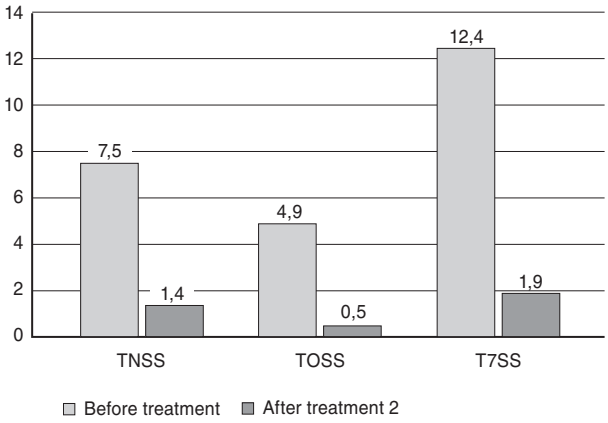


***Figure 1.*** **The dynamics *of* nasal and ocular symptoms before and after treatment with the drug (azelastine hydrochloride 140 mcg + mometasone furoate *50* mcg) according *to* the scales TNSS, TOSS, T7SS.**

*Table 2*

**Concomitant ENT diseases in patients with AR (M ± m)**

| Indicator | Abs (n = 10) | % |
|---|---|---|
| Chronic polyposis etmoiditis | 2 | 20 ± 12,6 |
| Chronic purulent haymoroetmoiditis | 1 | 10 ± 9,5 |
| Искривление носовой перегородки | 3 | 30 ± 14,5 |
| Deviation of the nasal septum | 3 | 30 ± 14,5 |
| Chronic tonsillitis | 2 | 20 ± 12,6 |
| Chronic subatrophic pharyngitis | 2 | 20 ± 12,6 |
| Chronic eustachitis, adhesive otitis | 1 | 10 ± 9,5 |

*Table 3*

**The indices of rhinomanometry in patients with AR before and after a test with a combined drug (azelastine hydrochloride 140 mcg + mometasone furoate50 mcg) (M ± m)**

| Indicators | Before test | 15 min post | 60 min post | After treatment |
|---|---|---|---|---|
| FIR, ml/s | 207,2 ± 55,9 | 150,9 ± 38,5 | 275,1 ± 60,2 | 323,6 ± 55,5 |
| FER, ml/s | 125,1 ± 23,1 | 130,4 ± 31,9 | 208,7 ± 56,9 | 293,6 ± 63,1 |
| RIR, кPa x s/l | 1,1 ± 0,2 | 1,3 ± 0,3 | 0,8 ± 0,2 | 0,7 ± 0,2 |
| RER, кPa x s/l | 1,6 ± 0,3 | 1,7 ± 0,5 | 1,3 ± 0,3 | 0,8 ± 0,3 |
| FIL, ml/s | 189,5 ± 33,4 | 210,8 ± 44,8 | 264,1 ± 41,8 | 320,1 ± 43,7* |
| FEL, ml/s | 132,9 ± 25,8 | 129,4 ± 27,8 | 216,6 ± 45,0 | 317,3 ± 61,4* |
| RIL, кPa x s/l | 1,0 ± 0,2 | 1,1 ± 0,2 | 0,7 ± 0,1 | 0,5 ± 0,1* |
| REL, кPa x s/l | 2,0 ± 0,9 | 1,4 ± 0,3 | 0,8 ± 0,1 | 0,7 ± 0,2* |
| FSUMI, ml/s | 360,6 ± 74,9 | 320,6 ± 66,2 | 516,8 ± 88,3 | 643,6 ± 71,9* |
| FSUME, ml/s | 246,3 ± 45,8 | 253,5 ± 48,0 | 410,8 ± 83,2 | 610,7 ± 109,3* |
| FSUMI, % after test | | 108,1 % | 168,4 % | |
| FSUME, % after test | | 155,2 % | 260,8 % | |

Note: * – statistically significant difference between results before and after treatment ($p < 0,05$).

After the end of treatment, all patients noted improvement in the quality of life: improvement of sleep, daytime activity, work activity, emotional state, which positively affected the personal life of patients. So the synonasal account according to the questionnaire SNOT-22 decreased from (54,0 ± 6,7) score to (21,9 ± 2,7) score, $p < 0,05$.

Combined endonasal spray (azelastine hydrochloride 140 mcg + mometasone furoate 50 mcg) well tolerated by patients. None of the subjects had any side effects.

## Conclusions

1. The combination of two drugs in a single device (azelastine hydrochloride 140 μg + mometasone furoate 50 μg) allowed to obtain early - from the 15th minute - improvement of the total nasal flow in the diagnostic rinomanometry test with the study drug in patients with moderate-to-severe AR. By the 60th minute, the increase in the total nasal flow on inspiration increased more than 1.5, on exhalation - more than 2.5 hold.

2. The presence of a pronounced improvement of total nasal flow in the early periods - from the 15th to the 60th minute from the beginning of the pharmacological test, allows to recommend the use of rhinomanometry in the test with combined drug mometasone furoate 50 μg/azelastine hydrochloride 140 μg in order to select patients for treatment with this combined drug.

3. Our research can not give the sufficient information on efficacy of treatment by the given medicine without comparison with other already existing endonasal GCS. Therefore, it is advisable to conduct further similar studies on a larger number of patients and compare the effectiveness of treatment with this combination drug according to the proposed method of selecting patients for treatment with other existing inhaled GCS.

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