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COMBINATION THERAPY FOR ALLERGIC RHINITIS: SEARCH FOR THE OPTIMAL SOLUTION

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ANNOTATION

Allergic rhinitis is a disease that is based on IgE-mediated inflammation of the nasal mucosa (caused by allergens), characterized by at least two of the following symptoms daily: nasal congestion, nasal discharge (rhinorrhea), sneezing, itching in the nasal cavity. Allergic rhinitis is often combined with other allergic diseases, such as bronchial asthma, allergic conjunctivitis, atopic dermatitis, and certainly is a global medical and social problem. Although allergic rhinitis is a serious, life-threatening disease, nevertheless, its medical and social significance is due to its high prevalence among children, adolescents and adults, especially in combination with acute and chronic sinusitis, otitis media and bronchial asthma.

Key words: allergic rhinitis, bronchial asthma, antihistamines, oral antihistamines, long-term and intensive treatment, diagnosis of allergic rhinitis.

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КОМБИНИРОВАННАЯ ТЕРАПИЯ АЛЛЕРГИЧЕСКОГО РИНИТА: ПОИСК ОПТИМАЛЬНОГО РЕШЕНИЯ

АННОТАЦИЯ

Аллергический ринит - это заболевание, в основе которого лежит IgE-опосредованное воспаление слизистой оболочки носа (вызываемое аллергенами), которое ежедневно характеризуется как минимум двумя из следующих симптомов: заложенность носа, выделения из носа (ринорея), чихание, зуд в полости носа. . Аллергический ринит часто сочетается с другими аллергическими заболеваниями, такими как бронхиальная астма, аллергический

конъюнктивит, атопический дерматит, и, безусловно, представляет собой глобальную медицинскую и социальную проблему. Хотя аллергический ринит - серьезное, опасное для жизни заболевание, тем не менее его медицинское и социальное значение связано с его высокой распространенностью среди детей, подростков и взрослых, особенно в сочетании с острым и хроническим синуситом, средним отитом, бронхиальной астмой.
Ключевые слова: аллергический ринит, бронхиальная астма, антигистаминные препараты, пероральные антигистаминные препараты, длительное и интенсивное лечение, диагностика аллергического ринита.

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ALLERGIK RINIT UCHUN KOMBINASION DAVOLASH: OPTIMAL DAVOLASH YO'LLARINI IZLASH

ANNOTATSIYA

Allergik rinit - bu burun shilliq qavatining IgE vositachiligidagi yallig'lanishiga (alergenlardan kelib chiqqan holda) asoslangan kasallik bo'lib, har kuni quyidagi belgilarning kamida ikkitasi bilan tavsiflanadi: burun tiqilishi, burun oqishi (rinoreya), aksirish, burun bo'shlig'ida qichishish. Allergik rinit ko'pincha boshqa allergik kasalliklar, masalan, bronxial astma, allergik konyunktivit, atopik dermatit bilan birlashtiriladi va bu global tibbiy va ijtimoiy muammo hisoblanadi. Allergik rinit jiddiy, hayot uchun xavfli kasallik bo'lsada, uning tibbiy va ijtimoiy ahamiyati bolalar, o'spirinlar va kattalar orasida, ayniqsa, o'tkir va surunkali sinusit, otitis media, bronxial astma bilan birgalikda tarqalishining yuqori darajasi bilan bog'liq.
Kalit so'zlar: allergik rinit, bronxial astma, antigistaminlar, og'iz antigistaminlari, uzoq muddatli va intensiv davolash, allergik rinit diagnostikasi.

Introduction. The prevalence of allergic rhinitis is from 10 to 40% of the population, and every year the number of patients suffering from this disease is increasing. According to epidemiological studies, in different regions of Russia 13.9–35% of the population suffer from allergic rhinitis, in England - 16%, in Denmark - 19%, in Germany - 17%. An increase in the prevalence of allergic rhinitis is associated with factors such as changes in lifestyle and diet [1, 2]. The minimal persistence of allergic inflammation of the nasal mucosa leads to more frequent viral and colds, which, in turn, contributes to an increase in the number of patients requiring long-term and intensive treatment, including in a hospital setting [1, 2].

Material and Methods: Allergic rhinitis undoubtedly reduces the quality of life of patients and motivates them to seek help from doctors of all specialties. All specialists should be aware that for the correct diagnosis of allergic rhinitis and the appointment of adequate therapy, it is necessary to conduct an allergic examination to identify a causal allergen. The cause of allergic rhinitis in the overwhelming majority of cases are household, epidermal, pollen allergens, spores of lower fungi, insect particles that enter the body by inhalation. Unfortunately, we have to state a significant underdiagnosis of allergic rhinitis in modern society, patients are treated symptomatically for a long time, without a correct diagnosis, only 18% of patients are referred to a specialist within the first year from the onset of the disease [3].

On the recommendation of WHO experts, patients with persistent allergic rhinitis should be screened for the presence of bronchial asthma. The main objectives in the treatment of allergic rhinitis are: achieving and maintaining control of the disease, eliminating symptoms, reducing the risk of complications and improving the quality of life of patients. Treatment of allergic rhinitis implies an integrated approach, while it is necessary to take into account the course, the severity of symptoms, individual social and psychological characteristics of the patient, concomitant pathology.

Allergic rhinitis is a common allergic condition. There are a variety of pharmacologic treatments, including antihistamines, oral decongestants, and intranasal corticosteroids. Leukotrienes cause significant nasal obstruction. Leukotriene receptor antagonists decrease symptoms and improve quality of life in patients with seasonal allergic rhinitis. Similar to antihistamines, antileukotrienes appear to be less efficacious than nasal corticosteroids.

Combination therapy of histamine and leukotriene antagonists produces symptomatic improvement as well as improved quality of life. Areas of study for combination antimediator therapy include expanding the initial findings with regard to nasal steroids, investigation of patient preference and compliance, use in perennial allergic rhinitis, and treatment of "one airway," i.e., treatment of concurrent allergic rhinitis and asthma.

Since their introduction in the 1940s, antihistamines (AHs) have been the most utilized class of medications for the treatment of AR. First-generation AHs are associated with adverse central nervous system (CNS) and anticholinergic side effects. On the market in the 1980s, newer generation AHs have improved safety and efficacy. Compared to antihistamines, intranasal corticosteroids (INCS) have significantly greater efficacy but longer onset of action. Intranasal AH and INCS combinations offer a single medication option that offers broader disease coverage and faster symptom control. However, cost and twice-per-day dosing remain a major limitation. Allergen immunotherapy (AIT) is the only disease-modifying option and can be provided through subcutaneous (SCIT) or sublingual (SLIT) routes. While SCIT has been the definitive management option for many years, SLIT tablets (SLIT-T) have also been proven to be safe and efficacious.

Antihistamines

For more than 72 years, antihistamines have been used for allergic rhinitis. The pathogenetic rationale for their use is the participation of histamine in allergic inflammation as the main mediator with a wide spectrum of biological activity. There are two groups of antihistamines - first and second generation. First generation antihistamines include: hydroxyzine, diphenhydramine, hifenadine, clemastine, mebhydroline, promethazine, chloropyramine.

Allergic rhinitis (AR) is an IgE-mediated inflammatory disease of the nasal mucosa, triggered by exposure to airborne allergens. It is estimated to afflict almost 25% of Canadians and has a significant impact on sleep, work, and school performance. AR is often associated with atopic dermatitis, food allergy, and asthma; this allergic disease progression known as the atopic march [2]. Symptoms primarily include rhinorrhea, nasal blockage, and sneezing, though ocular symptoms can also occur. In Canada, AR tends to be classified as either seasonal (SAR) or perennial (PAR) [3].

Standard of care for AR includes a treatment plan that considers patient preferences, the severity of the disease, and most essentially involves a shared decision-making process between patient and provider. Diagnosing AR and finding a care plan should consist of in-depth patient history, physical exam, and skin test to confirm allergies . The patient’s history should include evaluating nasal and ocular symptoms such as rhinorrhea, nasal itching, sneezing, allergic conjunctivitis, and nasal congestion . The timing of the onset of symptoms is essential in determining which allergens are suspect. A comprehensive review of concomitant medications such as nonsteroidal anti-inflammatory drugs, angiotensin converting enzyme (ACE) inhibitors, beta-blockers, and intranasal decongestants helps diagnose or rule out other causes of rhinitis . Concomitant atopic diseases such as asthma must be assessed as up to 40% of patients with allergic rhinitis, also have asthma .

Oral antihistamines

For decades, AHs have been the most utilized class of medications for the treatment of AR. AHs are inverse agonists; that is, they target H1 receptors (H1 antihistamines) at binding sites that are different from those of histamine [10]. There are two generations of oral antihistamines (first-, and newer-generation AHs), with newer-generation AHs being an improvement of their predecessor. First-generation AHs, such as diphenhydramine are associated with adverse central nervous system (CNS) side effects, including sedation and mental impairment, as well as anticholinergic side effects such as dry mouth, dry eyes, urinary retention, and constipation. Newer generation H1-antihistamines are safer than first-generation agents and should be the first-line antihistamines for the treatment of allergic rhinitis. However, for reasons that are discussed elsewhere, both patients and practitioners

continue to select first-generation AHs. This section aims to review the recognized risks of first-generation AH and to explore recent advances in newer generation AHs.

Adverse effects of first-generation AHs

The adverse effects associated with first-generation AHs have been reported since their introduction in the 1940s. Currently, it is well-known that these drugs have poor receptor selectivity and can bind non-selectively to several receptors in the body, including antimuscarinic-, anti-serotonin-, and anti-α-adrenergic receptors as well as cardiac potassium channels.

First-generation AHs can also cross the blood–brain barrier (BBB) and bind H1-receptors on neurons throughout the CNS and, therefore, may cause drowsiness, sedation, somnolence, and fatigue leading to impairment of cognitive function, memory, and psychomotor performances. The strong sedative qualities of older, first-generation AHs are why they are used as sleep aids. Paradoxically, the same dose is utilized to promote sleep as is used to relieve rhinitis symptoms.

Long-term, randomized, controlled studies of the safety of first-generation antihistamines are limited. However, many studies outline the association of these drugs with transportation-related injuries and fatalities. A recent review of toxicology tested profiles from 6677 fatally injured civil aviation pilots in the US from 1990 to 2012. In this study diphenhydramine was the most common drug found on autopsy capable of causing impairment (7.3%) [17]. As a result, first-generation AHs are now banned for use by commercial and military pilots before or during flights.Cardiac toxicity was previously an under-recognized risk of first-generation AHs. Diphenhydramine and hydroxyzine interfere with cardiac potassium channels involved in action potential repolarization. As a consequence, these drugs may cause dose-related prolongation and a form of polymorphic ventricular dysrhythmia called ‘torsade de pointes’.

The studies published to date demonstrate that leukotriene receptor antagonists are sometimes more effective than placebo, are no more effective than nonsedating antihistamines, and are less effective than intranasal corticosteroids in the treatment of allergic rhinitis. The combination of a leukotriene receptor antagonist and an antihistamine has not been proven to be more effective than either agent alone. This review reveals several inconsistencies that require resolution. First, whereas leukotriene receptor antagonists are predicted on the basis of their mechanism of action to improve nasal congestion significantly, clinical studies reveal leukotriene receptor antagonists to be no better than antihistamines at improving congestion. Second, leukotriene receptor antagonists would not be expected on the basis of their putative mechanism of action or nasal challenge data to improve significantly sneezing, nasal itching, or drainage. However, some studies show improvement in these symptoms during treatment with leukotriene receptor antagonists. Considered in aggregate, the data available to date do not clearly support a unique role of leukotriene receptor antagonists in the treatment of allergic rhinitis whether or not it is accompanied by asthma. They are characterized by low selectivity for H1 receptors and a short duration of action (within 4-12 hours). These properties are due to competitive and rapidly reversible binding to receptors and force the use of first-generation antihistamines in higher doses of 3-4 r. / Day to achieve a clinical effect. Second-generation antihistamines include acrivastine, loratadine, cetirizine, ebastine, rupatadine, bilastine - highly selective drugs with a duration of 18-24 hours. Also, second-generation drugs include active metabolites of known molecules: desloratadine, a metabolite of loratadine and rupatadine, levocetirizine, active isomerzine. cetirizine and fexofenadine are a metabolite of terfenadine.

The advantage of active metabolites is not only high selectivity, but also the absence of sedative and cardiotoxic effects. Second-generation antihistamines bind noncompetitively to H1-receptors, forming a ligand-receptor complex, which slowly dissociates, which causes a long half-life of the drug, allowing it to be used 1 r. / Day. One of the effective and safe antihistamines of the second generation is levocetirizine. Levocetirizine is a highly selective and potent antihistamines, is rapidly absorbed in the intestine, reaching a maximum plasma concentration in 0.5-1.0 hours after administration. Unlike most antihistamines of the first and second generation, levocetirizine shows systemic oral bioavailability of more than 77%, which indicates that the drug almost completely enters the systemic circulation. Levocetirizine is not metabolized in the liver and does not interact with cytochrome P450, therefore it has no competitive drug interactions. This makes it possible to

combine it with antibiotics, antifungal and other drugs and use it in patients with liver pathology. The ability to bind and the duration of communication with the H1-receptor in levocetirizine is 2 times higher than the affinity of cetirizine and approximately 30 times higher than the affinity of dextrocetirizine [4].

In the human body, levocetirizine does not undergo inversion, i.e., dextrocetirizine is not formed, which indicates the stability of the substance. Levocetirizine is 600 times more selective for H1 receptors than for other receptors and ion channels that are structurally similar, such as H2-, H3-, β- and β-adrenergic receptors, 5-HT1A and 5-HT2, dopamine D2, adenosine A1 and muscarinic receptors. Due to this, the drug has practically no anticholinergic and antiserotonin activity [5]. The listed parameters indicate the optimal pharmacokinetic profile of levocetirizine and determine its high clinical efficacy and high level of safety.

There have been many clinical studies proving the clinical efficacy and safety of antihistamines, where a pronounced positive effect on the severity of AR and the quality of life of patients was noted. The XPERT (Xyzal PErsistent Rhinitis Trial) study found that levocetirizine is highly effective and reduces the cost of long-term treatment. Also, when AR was combined with BA, the number of asthma attacks in the group of patients receiving levocetirizine significantly decreased [6].

Leukotriene receptor antagonist: For the treatment of AR, montelukast, a representative of the group of leukotriene receptor antagonists, can also be used, a highly effective drug that significantly improves inflammation indicators. Montelukast is rapidly and almost completely absorbed after oral administration. Regular food intake does not affect bioavailability and maximum plasma concentration. In adults, when taken on an empty stomach, montelukast is in the form of film-coated tablets at a dosage of 10 mg, the maximum concentration in the blood is reached after 3 hours.

The oral bioavailability of the drug is 64%. Montelukast is actively metabolized in the liver. It is assumed that cytochrome P450 CYP isoenzymes (3A4 and 2C9) are involved in the metabolism of montelukast, while montelukast does not inhibit cytochrome P450 CYP isoenzymes in therapeutic concentrations: 3A4, 2C9, 1A2, 2A6, 2C19, and 2D6 [7]. in diseases of both the upper and lower respiratory tract, it may be especially useful for patients suffering from AR in combination with BA. According to a retrospective study by Borderias et al., Montelukast was added to patients with asthma in combination with AR in addition to the previously prescribed basic therapy. According to the results of this work, the high efficiency of this therapeutic strategy has been confirmed in the form of better control over the clinical manifestations of both BA and AR [8].

Despite the significant progress in understanding the pathogenesis of the disease, one cannot but take into account such an important component of the treatment process as adherence to treatment. (compliance), that is, the correct fulfillment by the patient of all the doctor's recommendations on drug treatment, non-drug procedures, lifestyle changes, etc. Previously, it was believed that each patient actively fulfills the doctor's prescriptions, which in most cases was true. However, the situation gradually changed, and, according to a number of authors, cases of non-compliance with the recommendations received by patients have become more frequent [9].

Results and discussion: According to WHO estimates, about half of all patients do not follow the recommendations of medical professionals, which complicates treatment. The reasons for not following the recommendations are different: partial or complete refusal of treatment, irregular medication due to the upcoming side effects [9]. It is possible to significantly improve compliance if we take into account the individual characteristics of the patient, optimize the intake of the drug, reduce the frequency while maintaining efficiency and use fixed combinations.

Intranasal antihistamines

One concern regarding oral antihistamines (OAHs) is the possibility that OAHs cannot reach high enough concentrations in the nasal mucosa following oral administration to inhibit histamine-stimulated cytokine release and other mediators of early- and late-phase allergic reactions. Intranasal antihistamines (INAHs) ensure drug delivery to the nasal mucosa, enhancing local anti-allergic and anti-inflammatory effects while minimizing systemic exposure to therapy. The 2016 ARIA guidelines recommend using intranasal antihistamines (e.g., olopatadine, and levocabastine) in intermittent but

not persistent AR .While azelastine (AZE) is the most well-studied INAH, it is not available in Canada. However, levocabastine hydrochloride nasal spray (LEVO), another INAH, is available in Canada (see Table 1 for clinical usage information) and has shown to be equivalent to AZE in terms of efficacy and safety. In a recent multicenter, randomized, double-blind, parallel-group trial, 244 patients with moderate-to-severe allergic rhinitis were randomized to receive either AZE (0.1%) or LEVO for 14 consecutive days. Statistically significant changes from baseline in TNSS were seen in both treatment groups. No significant differences were seen between the two groups in terms of evaluation of therapeutic effect, total effective rate, and onset of action, except for a higher symptom relief rate in the LEVO group than the AZE group within 30 min of administering the first dose. Adverse reactions were mild to moderate, with an incidence of 0.9% for LEVO and 2.5% for AZE. In short, while intranasal antihistamines are safe and effective, only one is available in Canada and is often hard to obtain currently.

Intranasal corticosteroids

ARIA guidelines recommend INCS as the best option for both mild and moderate to severe AR in both children and adults . INCS inhibit the early and late-phase allergic in AR by preventing the recruitment of immune cells, and the release of inflammatory mediators from cells involved in the pathophysiology of AR . Many INCS have been approved since the introduction of beclomethasone in the late 1970s . All of the INCS currently available are efficient in controlling symptoms of AR, such as nasal congestion and itching, rhinorrhea, and sneezing .To differentiate products involves factors such as cost, ease of dosing, and sensory issues, such as aroma and taste, which can affect patient preference . As will be described in more detail below, the significant disadvantages of INCS are patient adherence and the length of time they take to reach maximal effect.

Safety of intranasal corticosteroids

INCS are less likely to display the systemic effects of oral steroids such as growth suppression, and ocular effects, due to reduced exposure and lower bioavailability. However, INCS are associated with mild to moderate local adverse effects. These include, epistaxis, nasal drying, burning, and stinging sensations. The literature examining the risk of development of glaucoma and/or cataracts from the use of INCS is also complex and controversial. While it is clear that inhaled and oral corticosteroid use is associated with high long-term risks of cataract development.the potential risk of cataracts with the use of nasal corticosteroids is more complex. Recently, a systematic review assessed whether the use of INCS is associated with increased intraocular pressure (IOP) above 20 mm Hg, glaucoma, or formation of posterior subcapsular cataracts in adult patients with rhinitis .A total of 484 studies were identified with 10 randomized controlled trials meeting the inclusion criteria. Meta-analysis of 2226 patients revealed that the use of INCS is not associated with a significant risk of elevating IOP or developing a posterior subcapsular cataract in patients with allergic rhinitis. The absolute increased incidence of elevated IOP in patients using INCS compared to placebo was 0.8% (95% CI 0 to 1.6%). There were zero cases of glaucoma in both placebo and INCS groups at 12 months. Future studies should formally evaluate for glaucoma rather than use IOP measures as a surrogate.

Efficacy of intranasal corticosteroids

Compared to placebo and antihistamines, INCS have significantly greater efficacy .This is further demonstrated in a systematic review comparing the efficacy of INCSs and OAHs that analyzed 5 controlled trials with a total of 990 patients. INCS were superior to OAHs in improving total nasal symptoms score and in relieving nasal obstruction, rhinorrhea, nasal itching, sneezing, and quality of life mean difference. However, there was no difference in relief of ocular symptoms .Similarly, Carr et al., compared the efficacy of AZE and fluticasone propionate (FP) in SAR via a post hoc analysis of data from a previously published direct-comparison study.

Intranasal antihistamine and intranasal corticosteroid combination

It is evident that no single medication class is without limitations (Table 1). The 2016 update of the ARIA guidelines does suggest (with low to moderate certainty) that combination treatment with an OAH or INAH and an INCS may be appropriate for patients with SAR. Indeed, the concurrent use of an INCS and INAH has provided benefits over monotherapy in patients with moderate-severe

SAR. The efficacy and safety of AZE/FP have been assessed in several controlled clinical studies. One 14-day SAR study compared AZE/FP with formulation- and device-matched AZE and FP. The AZE/FP combination provided greater overall nasal symptom relief than either FP, AZE, or placebo. More AZE/FP-treated patients achieved a 50% reduction in their overall nasal symptom burden. They did so many days earlier than those treated with FP or AZE.

The combination had an onset of action of 30 min, and the clinical benefit was observed during the first day of assessment and sustained over the entire course of treatment. AZE/FP was also compared to commercially available FP (Flonase generic) and AZE (Astelin®), respectively. The treatment difference was more considerable. When nasal and ocular symptoms were combined, AZE/FP was more than twice as effective as either FP or AZE. Likewise, patients reached a 50% reduction in their overall nasal symptom burden one week faster than those treated with FP or AZE. The long-term safety of AZE/FP has been evaluated in subjects with PAR or vasomotor rhinitis. There were no safety findings that would preclude the long-term use of AZE/FP in the treatment of allergic rhinitis .In patients who do not respond to INCS, a combination INAH/INCS should be considered, assuming cost is not prohibitive to the patient. Entropy or entopic end type is a new phenomenon discovered in allergology and immunology several years ago [6]. As our investigations showed, almost all parameters were the same as in healthy persons, and there are no systemic allergy signs. Nowadays, clinicians such as ENT specialists and lung physicians are involved in a discussion related to the diagnosis, treatment, and the relationship between local allergy and conventional or systemic allergy. Currently, the term "local rhinitis" is widely used, whereas there are only two references to "local asthma" [9, 10]. However, a positive response in "non-allergic" severe asthma was described [11, 12] that demonstrated the presence of atopic IgE-dependent inflammation in such patients.

Atopic conditions are characterized by heterogeneity and may accompany the covert or clinical food sensitization, which enables down regulating the course of any atopic disease. The identification of atopic end types will promote and drive innovative developments in both allergen-specific immunotherapy and anti-inflammatory approaches, including severe asthma.

Conclusion

AR remains an urgent problem due to its high prevalence, negative impact on the quality of life and frequent combination with other allergic diseases, including BA. Modern diagnostics and treatment of AR are an important area in the practice of doctors of many specialties: therapists, allergists, otorhinolaryngologists. Identification of allergic factors will allow diagnosing AR and choosing adequate prophylaxis and therapy, which will significantly improve the prognosis of the disease as a whole. The results of clinical studies have shown the high efficacy of levocetirizine and montelukast in the treatment of patients with AR, which makes it possible to include these drugs in therapy regimens. The possibility of using combined drugs with a single dosage regimen helps to achieve high adherence to treatment, increase doctor-patient cooperation. Thus, Montlesir is a promising drug that significantly expands the possibilities of choosing a doctor and patient in AR therapy.

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