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ORIGINAL PAPER

INTRANASAL CORTICOSTEROIDS OF THE NEW GENERATION IN THE THERAPY OF THE CHILDREN WITH ALLERGIC RHINITIS

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ABSTRACT

According to a recent epidemiological studies the avarage rate of prevalence of allergic rhinitis(AR) in children, in USA is between 20- 40% and in Western Europe up to 20%. The disease most ferquently appeared in children age 4 to 11. In this study authors analysed the results of the recent studies according to the literature data about the efficacy and safety of the intranasal corticosteroids in children with allergic rhinitis. These drugs as well as antihistamines and decongestants, are the first line therapy choice in allergic rhinitis. According to the numerous experimental and clinical studies, intranasal corticosteroids of the new generation decrease the intensity of allergic inflammmation by induction of apoptosis of eosinopils and by decreased expression of intercelular adhesion molecules (ICAM) and proinflammatory mediators as TNF-alpha, IL-8, Il-4, Il-5. All studies in children showed no significant bioavailability and no effect on plasma cortisol level in therapy with new generation of intranasal corticosteroids. The leading symptom of allergic rhinitis, nasal congestion, was markedly reduced.Intranasal corticosteroids decrease the intensity of simptoms in comorbid diseases in children as sinusitis, secretory otitis media and asthma attacks. The local adverse effects of intranasal corticosteroids such as iritabillity of nasal mucosa, dryness of the nose and mouth, headache and epistaxis are rare. The results of recent studies showed that intranasal corticosteroids of the new generations have high safety profile and are recommended as the first line therapy choice in children with moderate to severe type of persisent allergic rhinitis.

Key words: *allergic rhinitis, children, intranasal corticosteroids*

INTRODUCTION

Allergic rhinitis is IgE mediated allergic inflammation of the nasal mucosa.[1] According to a recent epidemiological studies of allergic rhinitis in children, the incidence of the disease ranged between 20 to 40% in USA and above 20% in Western Europe.[2,3] The peak of incidence was diagnosed in children age 4 to 11 year.[2,3] The major clinical signs are nasal congestion, rhinorrhea, itching, postnasal drip and cough. These complaints can detriment the quality of life decreasing the learning ability and attention and in the most severe cases causing sleep disturbancies in children.[1,2,3,4]

Typical clinical findings are: pale nasal mucosa with swollen turbinates, clear to white nasal secretions, and conjunctival injection or lacrimation. The diagnosis can be established through a focused medical history and physical examination with correlation of the patient's symptoms to positive results on skin-prick tests, IgE plasma concentration and eosinophils number in nasal smear. Comorbidities of allergic rhinitis include sinusitis, eustachian tube dysfunction with development of secretory otitis media, aggravation of asthma, and an increased likelihood of developing asthma due to increased airway inflammation and hyperresponsiveness.[6,9]

The clinical syptoms of allergic rhinitis are the result of complex patophysiology of allergic inflammation and disfunction of respiratory mucosa of upper and lower airways. The most recent studies sugessted the concept of the unified airway allergic disease. Allergic rhinitis is one of modalities of this clinical condition and could exist alone or being accompanied by other modalities known as comorbidities (asthma, secretory otitis media, sinusitis). It is well known that allergic rhinitis often coexisted with asthma, allergic dermatitis and conjuctivitis and in that way it can represent atopic constitution of the patient.[6,7]

Rhinosinusitis was diagnosed in over 70% of the patients with allergic rhinitis. According to some clinical CT studies of paranasal sinuses in allergic rhinitis, 77% pathological changes of ostiomeatal complex were found.[8] Persistant allergic inflammation cause the disfunction of mucocilliar clearance and oedema of the sinonasal mucosa. Nasal congestion, postnasal secretion, cough and headache are the major signs of the rhinosinusitis. Frequently, allergic inflammation of the sinuses were accompanied by exacerbation of the acute viral or bacterial inflammation.[9] Rhinosinusitis was more frequently diagnosed in persistent allergic rhinitis. Huang et al. pointed out that in the clinical studies of 251 children with persistent allergic rhinitis, rhinosinusitis was diagnosed in 46% but only in 4 % in the group of children with allergic rhinitis of the seasonal type.[10]

Secretory otitis media (SOM) is a disease that occurs in pre-school children clinically manifested as the presence of fluid behind an intact eardrum with conductive deafness, but no signs of acute inflammation. The disease is caused by different etiological factors: (morphological effects – cleft pallet, craniofacial anomalies, genetic defects of ciliary epithelia (Cartagen's syndrome), gastroesophaegal reflux, frequent infections of the upper respiratory tract with hypertrophy of the lymph tissue of the nasopharynx, hypertrophy of tubular tonsils, allergies, environmental factors – malnutrition and children fed only with synthetic baby food, as well as living in an environment full of dust, mold and cigarette smoke. Atopic constitution is a risk factor that four times more often causes the occurrence of SOM in children with allergies than in children that are not allergic .[11,12,13] Eosinophil cationic protein (ECP), mastocyte tryptase and myeloperoxidase of neutrophils have been identified in high concentrations in secretion and mucous membrane of the middle ear in children with allergy and secretory otitis.[12,13] Stimulation of the respiratory mucous membrane of the upper respiratory tract with an allergen and/or histamine leads to dysfunction of the Eustachian tube in more than 70 % of patients with allergic rhinitis. According to recent clinical studies the incidence of SOM in children with allergic rhinitis is between 40 to 60%.[13]

Allergic rhinitis is a risk factor for development of asthma. More than 40% of patients who suffer from allergic rhintis have asthma. Persistent type of allergic rhinitis more frequently cause asthma attacks than seasonal type of rhintis. Some studies claimed that more than 90% patients with asthma have had allergic rhinitis.[14] In the patients with seasonal allergic rhinitis and asthma,worsening of the symptoms of asthma was observed during the polen season.[14] Some studies examined the bronchial mucosa in nonasthmatic patients with allergic rhinitis. The bronchial mucosa specimens showed a slight increase in the basement membrane thickness and a presence of eosinophylic inflammation.The increase in airway responsiveness was recorded by nasal provocation tests in nonasthmatic patients with allergic rhinitis during pollen season.[14]

Results of the experimental studies with nasal provocation allergen test (grass polen) showed increased expression of intercellular adhesione molecules (ICAM) and increased number of eosinophils in nasal mucosa and nasal secretion and as well as in bronchial mucosa.[14] Similar results were confirmed by the experimental studies with bronhoprovocation tests. After bronchoprovocation test with grass polen, increased number of eosinophils and increased concentrations of IL 5 were recordeed in bronchial and nasal mucosa. The recent recomendation by ARIA association sugessted the simulteaneous therapy of the asthma and rinitis.[6]

Intranasal corticosteroids of the new generation (momethasone, fluticasone) (INCS) were recommended sa the first line therapy in the treatement of the allergic rhinitis in children.[14,15,16] The dilemmma concerning the duration of the therapy in always present when therapist precscribe corticosteroid drugs. The ground reason for selection of intranasal corticosteroid is limited number of local adversive effect and the lack of the evidence about sistemic adversive effect as confirmed by numerous clinical and experimental studies in last two decades.[14,15,16,17]

The aim of this study was to analyse the clinical benefit of the use of intranasal corticosteriods of the newer generation in the children with allergic rhinitis according to a recent cinical studies.

INTRANASAL CORTICOSTEROIDS AND ALLERGIC INFLAMMATION OF THE NASAL MUCOSA

The mediators of the early and late phase of allergic

Table 1. *The effects of intranasal corticosteroids in allergic inflammmation of nasal mucosa*[19,20,21,23]

Mediator/cell	The effect on cellular expression or mediator concentration
Eosinophyls	Reduction in number and apoptosis
Expression of ICAM, VCAM	decreased
Concentrations of proinflammmatory citokines (TNF alpha, IL-8)	decreased
Concentrations of citokines Il-4, IL-5	decreased
Concentrations of mastocyte triptase and eosinophyil cationic protein (ECP)	decreased

inflammation were frequently analysed in pathophysiology of allergic rhinitis. Increased permeability of the blood vessels, interstitial oedema of the nasal mucosa and disfunction of the sensory nerve endings appeared within few hours after interaction of allergen and IgE antibodies. Dominant effect in early phase of allergic inflammation of the nasal mucosa was mastocytes and basophyles degranulation and increased concentration of histamine, prostaglandins, leukotriens, bradykinine and substance P.This phase last of 4 to 8 hours after allergen challenge.[7,18,19] The activation of the immunocompetent cells is the crucial event in the late phase. Activated macophages, mast cells, eosinophils, lymphoplsmocytes , basophils and neutrophils produce increased concentration of leukotienes, prostaglandins and Th 2 cytokines (IL- 4, IL- 10). Increased expression of the intercellular adhesive molecules (ICAM) on epithelial cells and edothelial cells can additionaly enhance migration and activation of the immunocompetent acells. The final result is the amplification of the allergic inflammation of the sinonasal mucosa.[19,20]

The optimal pharmacoterapy of allergic rhinitis should maintain the reduction in number of the inflammatory cells and decrease the production of the mediators in nasal mucosa. The molecular effect of the intranasal corticosteroids in the inflammation of the nasal mucosa is still the subject of research studies. In vitro sudies which followed the level of molecular interaction between intranasal corticosteriod drugs and human recombinant corticosteroid receptor showed that momathasone had the strongest receptor affinity as compared to other drugs like fluticasone or budesonide (momethasone-1235, fluticasone 813, budesonide258).[22]

Clinical and immunohistochemical studies showed that local application of the newer generation of the intranasal corticosteroids results in apoptosis of the eosinolphyls. Decreased number of intraepitelial and subepithelial eosinophils in nasal mucosa specimens, as well as decreased number of basophils and lymphoplasmocytes was noticed in nasal mucosa after administration of the intranasal coticosteroids. [20,21,23] As a cosequence, the decreased concentration of mediators occurs such as decreased levels of tumor necrosing factor alpha (TNF alpha), interleukin 8 (IL 8), interleukins 4 and 5 (IL 4, IL 5) as well as decreased concentrations of mastocytes tryptase, eosinophilic cationic protein (ECP), leukotriens and prostaglandins. It was noticed that corticosteroids can inhibit the activation of nuclear factor kappa B(NF kB) which was recognized as one of the most important proinflammatory transcriptional factor in the process of allergic inflammation.[20]

The decreased expression of the intercellular adhesion molecules (ICAM) and vascular adhesion molecules (VCAM) on the surface of the endothelial and epithelial cells of the nasal mucoca was noticed after nasal mucosa was exopsed to intranasal corticosteroids (Table 1).[19,21,23]

Minshal et al. studied mucosal biopsies of the nasal mucosa in 69 patients with persistent rhinitis before and one year after continouus administration of the momethasone furoat in the daily dose of 200 μg. Immunochistoshemical analysis showed that prolonged administration of the momethason did not cause atrophy of the nasal mucosa. Comparison between mucosal biopsy specimens showed decresed number of intraepithelial and subepithelial eosinophils, as well as increse in number of cylindric cells of respiratory type one year after momethasone therapy. As conclusion, author emphasized that momethason has important role in the restitution of nasal mucosa.[21] Immunochistochemical studies of the nasal mucosa biopsies have not been studied so far in children with allergic rhinitis.

CLINICAL BENEFIT AND ADVERSIVE EFFECTS OF THE INTRANASAL CORTICOSTEROID THERAPY IN CHILDREN WITH ALLERGIC RHINITIS

According to a recent clinical studies the corticosteroids of the new generation (momethasone, fluticasone) can be very effective in reduction of nasal congestion, anterior and posterior nasal drip and cough.[7,15,16,17] The crucial reason for the use of intranasal corticosteroids of the newer generation is local administration without sistemic adversive effects. Systemic adverse effects of active corticosteroids are:osteoporosis, glaucoma, cataracts, adrenal suppression, and impaired growth in children.The newer intranasal corticosteroid(INCS) drugs have been found to have no adverse effects on growth and hypothalamic-pituitary-adrenal-axis function in children.[16,17]

After administration of the first dose of INCS initial clinical signs occured between 4 to 12 hours. Clinical studies showed that initial reduction of the nasal congestion occured 5 hours after momethasone administration and reached complete reduction of nasal congestion 36 hours after in patients with seasonal allergic rhinitis. Momethasone was administered in the daily dose of 200 μg.[25] Significant decrease of total nasal syptom score was observed third day after INCS administration.[25] Efficacy studies performed in children with seasonal type of alergic rhinitis recommended as optimal daily dose of 100 μg during 2 weeks.[15, 16,17]

In 544 children age 2 to 11 years with seaseonal allergic rhinitis the reduction of total nasal score (congestion, itching, posterior and anterior nasal drip) was significantly reduced as pointed out by Meltzr. The terapy consisted of fluticasone given in daily dose of 110 μg during two weeks.[27] Intranasal corticosteroids of newer generation could be used as profilactic therapy in patients with moderate to severe seasonal allergic rhinitis. In 61 patients age 12 to 57 years, Pitsios et al. were administered momethason in single daily dose of 200 μg. According to the results of this study 78% of patients have had minimal simptoms of allergic rhinitis at the starting point of polen season with daily total nasal score less than 1.4.[28] Similar studies have not bee yet published in children with allergic rhinitis.

Therapy with INCS in severe forms of persistent allergic rhinitis was analysed in a few studies. Skoner et al. measured cortisol plasma level and growth index in 59 children age 4 to 10 years with persistent rhinitis. The patients were terated by fluticasone in daily dose of 200 μg during 14 days with wash out period of 14 days. Results of this study pointed out safety of this therapy shedule with no significant increse in plasma cortisol level and no influence in growth index of terated patients.[29] Similar results were published by Schenkel et al. Study included 98 children with persistent allergic rhinitis age 3 to 9 years treated with momethasone in daily dose of 100 μg. The duration of the therapy was one year.[30] Galant et al. analysed the cortisol level during six week therapy in children age 2 to 3 yers with persistent allergic rhintis which were administered fluticasone in single daily dose of 100μg. The results of this study showed no increse in daily plasma corticole level, no growth disturbances and no pathological findings during ophtalmoscopy.[31] The potential for systemic activity INCS might be explained by nasal epithelium absorbtion or by absobtion trough gastrointestinal tract. Low nasal and gastrointestinal absorbtion rate and fast first pass hepatic inactivation are important paharmacokinetic properties of INCS of newer generation. After oral administration the fraction of drugs which become bioavailable was measured for beclomethasone, fluticasone and momethasone. The bioavaliibilty rate ranges from 41% to 11% for beclomethasone to less than 1% for momethasone and fluticasone. [31,32] Some of the studies showed that beclomethasone dipropionate intranasal spray caused significant growth suppression of 0.9 cm after one year of the drug administration in doses of 168 mcg BID in children with allergic rhintis.[32]

Local adversive effects appeared in the interval between 5 to 10 % after intranasal administration of momethasone and fluticasone longer than 4 weeks. Studies that followed INCS administration in two weeks interval in children with seasonal allergic rhinitis reported local adversive effects in the frequency less than 2%.[30,31,32,33]

Headache, burning nose, bad taste, somnolence or insomnia, sangvinolent nasal discharge or epistaxis are the local adversive effects that were most frequently reported. Vasoconstriction is the main pathophysiological mechanism that cause mucosal dryness and epistaxis after prolongued administration of INCS. The most severe complication as perforation of the nasal septum was rarely described in adult patients but there is no reports about that complication in children. Before the therapy has been started, parents should be given all information about adversive effects of INCS. If any of afore- mentioned adversive effects apeared parents must be informed to stop further administration of the INCS and to bring child to control examination. Daily doses that were recomended for pediatric population with allergic rhinitis are 100μg up to 14 days. This therapy shedule was recomended as one with minimal or no local adversive effects at all.[17,30,31,32,33] In the case of prolonged therapy with INCS , frequent control examinations were recomended, each 14 days. The therapy duration depends on

simptoms of the disease and it should be individually adjusted according to oscillation in intensity of simptom nasal score of AR. The results of recent studies showed that intranasal corticosteroids of the new generations have high safety profile and are recommended as the first-line therapy choice in children with all forms of allergic rhinitis especially in children with moderate to severe type of persisent allergic rhinitis.

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