UDC 616-004.6. 616-022.7/.9. 616-08-031.84

A MODERN VIEW ON PATHOGENETIC THERAPY OF ATOPIC DERMATITIS IN CHILDREN (LITERATURE REVIEW)

Khaitov K.N., Abidov A.M., Abidov Kh.A. Karimov B.B.

Tashkent Pediatric Medical Institute

✓ ***Resume***

The article presents modern views on rational therapy for atopic dermatitis in children. The issues of the use of antihistamines and topical anti-inflammatory drugs are discussed. Among the latter, special attention is paid to methylprednisolone. The analysis of the use of methylprednisolone aceponate in the treatment of atopic dermatitis in children was carried out. It also provides research data on the effect of the desloratadine on the course of atopic dermatitis in children. It has been shown that the inclusion of the drug in the complex therapy of atopic dermatitis in children provides a rapid clinical effect.

Keywords: atopic dermatitis, children, allergies, treatment, external therapy, antihistamines, glucocorticosteroids

СОВРЕМЕННЫЙ ВЗГЛЯД НА ПАТОГЕНЕТИЧЕСКУЮ ТЕРАПИЮ АТОПИЧЕСКОГО ДЕРМАТИТА У ДЕТЕЙ (ОБЗОР ЛИТЕРАТУРЫ)

Хаитов К.Н., Абидов А.М., Абидов Х.А. Каримов Б.Б.

Ташкентский педиатрический медицинский институт

✓ ***Резюме***

В статье представлены современные взгляды на рациональную терапию атопического дерматита у детей. Обсуждаются вопросы использования антигистаминных и топических противовоспалительных препаратов. Среди последних особое внимание уделено метилпреднизолону. Проведен анализ применения метилпреднизолонаацепоната в лечении атопического дерматита у детей. Также приводятся научно-исследовательские данные по изучению влияния дезлоратадина на течение атопического дерматита у детей. Показано, что включение препарата в комплексную терапию атопического дерматита у детей обеспечивает достижение быстрого клинического эффекта.

Ключевые слова: атопический дерматит, дети, аллергия, лечение, маҳаллий даво, антигистаминные препараты, глюкокортикостероиды

БОЛАЛАРДА АТОПИК ДЕРМАТИТНИ ПАТОГЕНЕТИК ДАВОЛАШНИНГ ЗАМОНАВИЙ ТАМОЙИЛЛАРИ (АДАБИЁТЛАР ШАРҲИ)

Хаитов К.Н., Абидов А.М., Абидов Х.А., Каримов Б.Б.

Тошкент педиатрия тиббиёт институти

✓ ***Резюме***

Мақолада болаларда атопик дерматитнинг рационал даволаш бўйича замонавий маълумотлар келтирилган. Антигистамин ҳамда маҳаллий яллигланишга қарши дори воситаларини қўллаш масалалари муҳокама қилинган. Иккинчи гуруҳ орасида метипреднизолонгаалоҳида этибор қаратилган. Болаларда атопик дерматитни даволашда метилпреднизолон ацепонатдан фойдаланиш бўйича таҳлиллар келтирилган. Шунингдек, дезлоратадиннинг болаларда атопик дерматитнинг кечишига таъсирига доир илмий-тадқиқот маълумотлар келтирилган. Болаларда атопик дерматитни комплекс даволашда ушбу препаратни қўллаш тезкор клиник таъсир кўрсатишига олиб келади.

Калит сўзлар: атопик дерматит, болалар, аллергия, даволаш, иммунитет, антигистамин дори воситалари, глюкокортикостероидлар

Relevance

In recent years, the problem of atopic dermatitis (AD) in children has been acquiring more and more medical and social significance, since the prevalence of the disease is growing steadily, making up in various countries of the world from 6% to 25% [2, 11,

Atopic dermatitis remains one of the most pressing problems in dermatology due to the widespread and growth of this dermatosis, severe course, insufficient effectiveness of existing treatment methods [33, 39].Atopic dermatitis (AD) is one of the most common human diseases. The increase in morbidity in the last decade, a chronic course with frequent relapses, insufficient effectiveness of existing methods of treatment and prevention put blood pressure among the most pressing problems of modern medicine [31]. Atopic dermatitis occurs, as a rule, in early childhood in persons with a hereditary predisposition to atopic diseases, has age-related characteristics of the localization and morphology of foci of inflammation.

Atopic dermatitis is a chronic disease, which is based on IgE-dependent inflammation of the skin and its hyperreactivity, disrupting the natural reaction of the skin to external and internal irritants. AD, as a rule, debuts in early childhood and is characterized by a severe, persistent course, frequent relapses and the development of complications [36].

The causes of atopic dermatitis are not fully understood. At various stages of AD teachings, it was invited to many concepts of disease. Basically, they reflect three hypotheses: constitutional predisposition, psychosomatic and allergic (immunological) [3, 10, 42].

The mechanisms involved in the pathogenesis of AD are multifaceted. Hereditary predisposition, disturbances in the activity of the central and autonomic nervous systems, disturbances of the immune system, metabolic, neuroendocrine and neurovascular disorders, disturbances in the functioning of the gastrointestinal tract, inappropriate nutrition, various intoxications, the influence of unfavorable environmental factors - all this together determines onset of the disease, chronic course of AD or aggravates its course [12, 26, 34].

The mechanisms of genetic predisposition are not entirely clear. It is believed that the following features of the immune system can lead to the development of atopy: direct switching of B cells to the synthesis of IgE antibodies, overproduction of key cytokines by T cells, structural features of receptors for these cytokines, and impaired formation of regulatory cells. How significant is the participation of each of these mechanisms remains poorly understood [36, 43].

Complex pathogenesis, multiple organ lesions in atopic dermatitis require an integrated approach in the treatment of patients with AD. Therapy of atopic dermatitis still continues to be one of the most difficult tasks in clinical practice. External therapy in the treatment of patients with atopic dermatitis plays an essential role: it is widely used both in complex therapy and independently [4, 43, 58].

The relevance of further study of atopic dermatitis is determined not only by the high prevalence and significant increase in the incidence of this dermatosis, but also by the inconsistency in the assessment of various pathogenetic mechanisms of its development and, as a consequence, to an insufficiently effective treatment of this dermatosis.[10, 43].

The pathogenesis of AD is based on immune mechanisms with the leading role of T-lymphocytes and Langerhans cells. The latter are the main cells of the skin's immune system, responsible for IgE-mediated accumulation of allergens in the skin and their presentation to T-lymphocytes. The number of Langerhans cells in patients with AD is significantly higher than in healthy ones. In addition, Langerhans cells play an important role in maintaining the mitotic activity of keratinocytes at a low level due to the initiation of apoptosis, which limits their pronounced proliferation [54, 56].

In recent years, Langerhans cells have been considered as specialized highly potent antigen-presenting cells of bone marrow origin. At the first contact, the antigen binds to high-affinity IgE receptors, which are located on the surface of Langerhans cells, in which the allergens undergo enzymatic cleavage and bind to HLA class II. The resulting polypeptide is specifically recognized by the T-cell receptor of CD4 + lymphocytes.Having received information, Langerhans cells move to the lymph nodes, where they interact with Th0-lymphocytes, which increases the activation of T-helpers, promotes their switching towards Th2 and is accompanied by an increase in cytokine production. In this case, Th2-helpers secrete mainly IL-4, IL-5, IL-10, IL-13 and activate B-lymphocytes with local overproduction of specific IgE [36, 37].

When the allergen re-enters, it binds to specific receptors on the membrane of mast cells, which causes degranulation of the latter with the release of inflammatory mediators and chemokines, which trigger the early phase of an

allergic reaction, clinically manifested by severe itching, hyperemia, and rashes. Under the action of IL-5, IL-6, IL-8, there is an increase in the migration of eosinophils and macrophages to the inflammation focus, which determines the rate of chronicity of allergic skin inflammation. Long-lived eosinophils, which are less susceptible to apoptosis and produce high levels of the main protein of eosinophils, are also important in the chronicity of AD; Th1-helpers are also activated with predominant production of interferon γ (IF-Hγ) [1, 37].

This process of "switching" Th2 cells to Th1 is associated with increased production of IL-12, which contributes to the chronicity of the allergic process in the skin [2, 12]. Along with the immune mechanisms in the pathogenesis of AD, damage to the stratum corneum of the epidermis and the water-lipid film as a result of allergic inflammation, leading to severe dryness of the skin, is important. Increased dryness of the skin contributes to the maintenance of itching, and itching and scratching are accompanied by additional damage to keratinocytes and mast cells, which increases allergic inflammation of the skin. Combs contribute to skin infection with pathogenic flora, mainly Staphylococcus aureus. Along with this, the gradually developing dysfunction of the nervous system, which, through neuropeptides, is directly involved in the mechanisms of the formation of itching and other manifestations of AD in children, is of paramount importance.[4, 57].

At AD, allergic inflammation develops, in which the water-lipid film and the stratum corneum of the epidermis are damaged, which significantly reduces the barrier functions of the skin and increases the risk of secondary infection. At the same time, trans epidermal water losses significantly increase, which leads to pathological dryness of the skin, increased itching, impaired physiological desquamation of the epithelium, thickening of the stratum corneum with the development of hyperkeratosis and pronounced desquamation, which determines the importance of external therapy for blood pressure in children.

The current strategy for the treatment of patients with atopic dermatitis (AD) includes the control of provoking factors, patient education, diet therapy, topical and systemic complex pharmacotherapy [18]. Among the means of systemic action, the leading place belongs to antihistamines (AHP). The widespread use of AGPs is due to their ability to reduce itching of the skin and the intensity of allergic inflammation. Despite the fact that the antipruritic effect is generally more pronounced in AHP of the first generation (AHP with a sedative effect), for long-term basic therapy of AD, only AHP devoid of the properties of tachyphylaxis, i.e., drugs of the second generation, can be used. Long-term course use of AHP is aimed at achieving an anti-inflammatory effect and inhibiting the development of a chronic process [16].

Histamine, according to both experimental and clinical studies, is one of the key components of the pathogenesis of allergic reactions and one of the most powerful pruritogens. In addition, histamine acts as a regulator of the synthesis or release by cells of some other biologically active substances (acetylcholine, serotonin), or itself, perhaps, one of the final effector molecules that mediate, for example, the action of substance P [50].

Antihistamines of the second generation, in particular desloratadin, are traditionally used in the complex therapy of itchy dermatoses, especially of an allergic nature. Modern knowledge suggests that using antihistamines, we achieve not only a direct effect of disrupting the interaction of histamine with its receptors, but also indirectly affect the metabolism and expression of other mediators of pruritogenesis [50]. In addition, prolonged use of modern antihistamines leads to a change in the permeability of the vascular wall, a decrease in the concentration of chemoattractants, as well as other biologically active substances in the focus of allergic inflammation, i.e., it has an anti-inflammatory effect [13].

The anti-inflammatory effect of desloratadine, independent of its antihistamine action, is realized through the suppression of a number of key mechanisms responsible for the severity of the early and late phases of the allergic reaction. So, desloratadine:

• reduces the intensity of release and / or expression by mast cells, basophils, endothelial and epithelial cells of the following substances - histamine, cytokines, chemokines, arachidonic acid derivatives, tryptase, cell adhesion molecules;

• inhibits adhesion and chemotaxis of eosinophils, their production of superoxide [24].

The efficacy and safety of desloratadine in the treatment of mild to moderate AD in children has been evaluated in many clinical studies [15]. It has been shown that this drug causes a decrease in the severity of not only itching, but also such manifestations of the disease as erythema, edema, papular rashes, excoriation [17].

Among the drugs for the treatment of atopic dermatitis (AD) in children, antihistamines are a mandatory component of therapy. As a pathogenetic therapy, histamine blocking therapy, as well as aimed at strengthening and stabilizing mast cell membranes, can be used. Until recently, the leading role in the treatment of atopic dermatitis was played by antihistamines of the first generation, the main used effect of which was the blocking of histamine receptors. Unfortunately, these drugs have a number of side effects. In particular, they cause drowsiness, a feeling of fatigue, impaired coordination of movements, concentration of attention, dizziness, headaches, and decreased blood pressure [20]. Antihistamines of the second and third generation are devoid of these side effects. At the same time, third-generation drugs are several times more active than second-generation drugs [19].

Today, antihistamine drugs of a new generation are considered as drugs of choice, which differ from drugs of the old generation by the presence of anti-inflammatory activity and the absence of sedative action [7, 8, 35]. Modern antihistamines are represented by active metabolites (Eden, fexofenadine, desloratadine, levoEdem) and prodrugs (loratadine, ebastine) [32, 49].

One of the most effective representatives of the former is desloratadine, an active metabolite of loratadine, a well-known second-generation selective blocker of H1-histamine receptors. Currently, the pharmaceutical company Farmak produces desloratadine under the name Edem. Among modern antihistamines that are active metabolites, Eden was the first to be created. Eden is a metabolite of hydroxyzine (Atarax). More than 15 years of clinical experience in the use of Eden and many experimental and clinical studies have demonstrated its high efficiency and safety [7].

There is an opinion among doctors that when using the drug in the form of a syrup, allergic reactions occur more often. In this regard, a study was conducted in Russia, the purpose of which was to assess the efficacy and safety of the use of the drug Edem in the form of a syrup in children with AD [32]. An open, non-comparative study was conducted, which included 36 children aged 2 to 6 years with AD. The work was attended by pediatric allergists of outpatient allergy rooms with more than 10 years of experience in their specialty. The introductory period was 7 days, during which only non-steroidal external agents were allowed for use. During the entire study period and a week before it was prohibited from taking any antihistamines, including ketotifen, as well as glucocorticosteroids in any form [8, 14].

A study to study the safety of the use of Eden and the effectiveness of its effect on the leading clinical and anamnestic manifestations in atopic dermatitis in childhood showed that all children with skin hyperemia and cutaneous hemorrhagic elements of atopic dermatitis underwent a complete reverse development. Significant positive dynamics under the influence of Eden was also registered in relation to papular allergic eruptions in persons with concomitant chronic pathology of the gastrointestinal tract.In particular, none of them showed the appearance of new elements of the rash. In 89.1% of patients in this group, including children with neurodermatitis and eczema, the rash turned pale. In 10.9% of cases, its complete extinction was stated. The study proved the presence of a significant antihistamine effect in the drug Edem, caused not only by the blockade of histamine H1 receptors, but also by a decrease in the release of the latter from mast cells as a result of stabilization of their membranes. The established circumstances make it possible to recommend Eden as a highly effective and safe treatment for various pathogenetic variants of atopic dermatitis in childhood [6].

Against the background of the therapy, which included adherence to a hypoallergenic diet and the use of non-steroidal external agents, by the beginning of treatment with Eden, the pruritus index and the SCORAD index were 5.4 and 44.8 points, respectively. By the end of the second week of treatment with Eden, the pruritus index decreased 2 times and amounted to 7 points, and the SCORAD index value - almost 2 times and amounted to 3.6 points. However, these differences were statistically insignificant. All other indicators also showed positive dynamics by the end of the second week of treatment. After completion of the 4-week course of treatment with Eden, all indicators significantly (statistically significant) decreased. The index of the prevalence of the skin process decreased by 58,0% and amounted to 3 points compared to 5.5 points before the start of treatment. The index of the intensity of the skin process decreased by 71.6% and amounted to 9.0 points compared to 31.7 points before the start of treatment. One of the convincing proofs of the high clinical efficacy of the drug in AD in children is the rapid dynamics of reducing pruritus and improving sleep. The intensity of itching decreased by 87.0% and amounted to 0.7 points versus 5.4 points before treatment. Sleep quality improved by 95.5%, amounting to 0.1 points compared to

2.2 before the start of treatment. Sleep returned to normal as itching subsided. The SCORAD index decreased by 71% by the end of the 4-week course of treatment with Eden and was 1.9 points compared to 44.8 points at the beginning of treatment. Thus, a 4-week course of treatment with Eden syrup in children with AD at the age of 6 years has achieved significant clinical improvement. The drug was well tolerated. No side effects associated with the intake of Eden have been registered [5].

The use of desloratadine in the form of a solution and syrup in the complex therapy of AD in young children ensured a rapid achievement of a clinical effect, primarily due to a decrease in erythema, edema / weeping, itching and excoriation. Both subjective and objective symptoms of AD were clearly reduced. Our clinical observation results are consistent with previously published data [9, 27]. It should be emphasized that in the study by N.A.Geppe et al. [9] observed children aged 2–5 years with mild to moderate AD. The present clinical observation demonstrates the high efficacy of desloratadine in the complex therapy of AD in children aged 12 to 24 months with a disease of moderate severity and severe course.It is noteworthy that, in spite of the indicated differences in the observation groups, in two studies, similar results were obtained regarding the symptoms of AD, especially the timing of the onset of a stable therapeutic effect. So, in the study of N.A. Geppe et al. the first signs of improvement were noted in children with moderate AD from the 2nd week of treatment, but significant or complete suppression of all symptoms by the end of the 3rd week of treatment with desloratadine [9]. Likewise, according to the results of our work, we would like to emphasize the most complete effect of desloratadine on all clinical symptoms of AD at treatment periods from 2 to 4 weeks. Of course, this indicates the advisability of including desloratadine in the treatment of AD in young children only as a means of basic, long-term therapy. For clinical practice, it is important that we revealed the absence of differences in the main parameters of the efficacy and tolerability of the two forms of desloratadine - the original drug in the form of a syrup and a generic drug in the form of a solution. Such a comparative study of the efficacy and tolerability of desloratadine in 2 forms in children from 12 months of age has not yet been carried out.

External therapy- an integral part of the complex treatment of blood pressure in children. It should be carried out differentially, taking into account pathological changes in the skin and the use of topical drugs and their various forms [1, 59]. Rational and timely use of topical means of external therapy for AD, in essence, determines the rate of reverse development of skin inflammation, and in parallel with the extinction of skin symptoms, subjective sensations - itching, burning and discomfort of the skin, improve significantly and the mood and quality of life of a sick child.

External treatment is reduced to relieving inflammation and itching by prescribing anti-inflammatory drugs. The purpose of the external treatment is to improve the barrier function of the skin and restore the water-lipid layer with the help of emollients and nourishing agents and to ensure proper daily skin care by prescribing cleansers and moisturizers.

With an exacerbation of AD, it is necessary to stop inflammation and itching by prescribing external anti-inflammatory drugs containing topical glucocorticoids (GC) or non-steroidal anti-inflammatory drugs. In severe cases and severe exacerbation of AD, it is necessary to use topical GCs, which act on all inflammatory cells, including Langerhans cells, have a pronounced anti-inflammatory effect and are the modern standard of anti-inflammatory therapy. GCs is prescribed in the acute period of AD in short courses of 5–7 days, and in chronic course according to the intermittent method every other day or 2 times a week. To increase the effectiveness of topical GCs in the treatment of AD, it is advisable to use them against the background of emollients and nutrients.[21, 26].

GCs is prescribed for severe AD, with a pronounced exacerbation of blood pressure in both acute and chronic course, with ineffectiveness of anti-inflammatory nonsteroidal therapy for AD for 3-5 days [26, 28].

To standardize the clinical effect and conduct a study of the effectiveness of drugs, the clinical effectiveness index (CI) was introduced. CI = clinical index of treatment was assessed in points according to the following signs: 0 - no effect; 1-improvement; 2 - significant improvement; 3 - re-mission. Such a simple approach will make it possible to develop a specific algorithm for choosing a drug for treatment [29].

Along with topical emollients, current approaches to the treatment of AD include topical corticosteroids (TC) and topical calcineurin inhibitors (TICs). TC are recommended as first-line agents for the treatment of acute and chronic inflammatory processes in AD, as well as as initial therapy drugs for moderate and severe forms of the disease. MC suppress 3 main components of the development of allergic

inflammation: the release of mediators (histamine, leukotrienes, prostaglandins), cell migration to the affected area and cell proliferation at the site of inflammation. As a result, MCs have a complex anti-inflammatory, anti-excretory and immunocorrective effect. Therefore, TC are the drugs of choice in the treatment of exacerbations of the disease, because affect the early and late phases of allergic inflammation, prevent the development of a systemic immune response with the involvement of conjugated target organs (respiratory, digestive, etc.)[30, 38, 44, 46].

Why treatment with topical glucocorticosteroids should not be postponed:

1. It is important to use TC at the first signs of AD, to apply the drug to all foci of inflammation until the symptoms are completely relieved.

2. Interruption of the course of treatment until complete control is achieved is associated with the development of new exacerbations.

3. Lack of adequate therapy leads to a prolonged course of AD, involvement of other areas of the skin and the addition of a secondary infection.

Side effects when using TC can occur when the mode of their use is violated. With prolonged application of halogenated drugs, especially on large surfaces (more than 10%) and / or highly sensitive areas of the skin (eyelids, neck, folds), the development of stretch marks, telangiectasias, skin atrophy, and among the systemic side effects - hypertension, hyperglycemia [41, 45, 53, 55].

It is possible to reduce the risk of side effects with the use of drugs that act only in the focus of inflammation. For halogenated drugs, a continuous course of steroid therapy should not exceed 2 weeks, and if indicated, an intermittent course should be used (2-week break after 2 weeks of therapy) [45, 48, 55].

According to the strength of their influence on the allergic inflammatory process, TC in Europe are divided into 4 classes (Table 1).

In patients with severe exacerbation of AD with localization of foci of allergic inflammation on the extremities and trunk, TC treatment is started from class III. For the treatment of sensitive skin areas, preference is given to non-halogenated TC or non-steroidal drugs - calcineurin inhibitors. Class IV drugs are not recommended in children under 14 years of age.

The minimum allowed age for the use of TC: Advantan® from 4 months 1 r / day (it is possible to safely apply the original drug to an area of up to 60% or within 4 weeks), for alclomethasone (contains halogens) from 6 months of age 1–3 r / day and for mometasone from 2 years of age 1 r / day [40, 51]. From TC in pediatric practice, preference is given to drugs with minimal side effects while maintaining a high degree of anti-inflammatory action. In this regard, the optimal use of the latest generation of TC - methylprednisolone aceponate (Advantan) [48, 55].

Table 1. Classification of topical glucocorticosteroids by degree of activity (Miller & Munro, 1980, with additions)

Class (degree of activity)	International non-proprietary name
Stage I (weak)	Hydrocortisone (hydrocortisone acetate) 0.5%, 1% ointment Prednisolone 0.5% ointment
Stage II (mediumstrength)	Alclomethasone (alclomethasonedipropionat), 0.05% ointment, cream
III stage (strong)	Methylprednisolone aceponate 0.1% (Advantan®) cream, emulsion, fatty ointment, ointment Mometasone (mometasone furoate 0.1% ointment, cream, solution) Triamcinolone acetonide 0.1% ointment Fluocinolone acetonide 0.025% - naya ointment, cream, gel, liniment Fluticasone (fluticasone propionate), 0.005% ointment and 0.05% Betamethasone cream (betamethasone valerate, betamethasone dipropionate, 0.1% cream and ointment; 0.05% - cream and ointment) Hydrocortisone (hydrocortisone butyrate, 0.1% ointment, cream, emulsion, solution)
IV stage (verystrong)	Clobetasol 0.05% cream, ointment

It is taken into account that TC are better absorbed in areas of inflammation and desquamation, they penetrate significantly better into the thin stratum corneum of the skin in young children, as well as anatomical areas with a thin epidermis. Occlusive dressings help to

moisturize the skin and significantly, by a factor of 100, increase the permeability and activity of TC. The ointment base of the drug increases the absorption of the active substance, having a more powerful effect than creams and lotions [40, 41, 45, 46, 51].

Taking into account the peculiarities of the pathological process of AD in children and the anatomo-physiological characteristics of children's skin, preference should be given to preparations in the form of an emulsion and cream. General contraindications to TC prescription are individual intolerance, infections (viral, bacterial, fungal), acne, rosacea, pregnancy (not for all drugs), lactation (not for all drugs) and skin tumors.

A multidisciplinary approach and education of patients and their families in the rules for taking TC and proper skin care is of fundamental importance. There is an obvious need, due to the practical significance, to use the developed method of TC dosing, depending on the localization of AD and the patient's age (Table 2).

Class III local TC have an optimal benefit / risk ratio. A special place in the practice of a pediatrician is occupied by methylprednisolone aceponate (Advantan), which is allowed from the age of 4 months.

Methylprednisolone aceponate (MPA) is a non-halogenated dietary 6-alpha-methylprednisolone, the high activity of which is associated with the introduction of a methyl group in the CG position. Unlike most strong halogenated MCs, the C6, C9 and C12 positions are free of fluorine and chlorine, which leads to a minimum of local and systemic side effects. Double esterification provides high lipophilicity of the molecule, the implementation of rapid permeability through the stratum corneum of the epidermis and a high therapeutic concentration in the dermis. The accumulation of the drug in the stratum corneum does not occur, so there are no side effects.

Table 2. Dosage of glucocorticosteroid for different parts of the body depending on age

Child's age Skin surface area	FTU (dose, units)	TC (doseingrams)
4-12 months		
Face + neck	1	0,5
Wholearm + brush	1	0,5
Front surface gr. cells + belly	1	0,5
Back + buttocks	1,5	0,75
Wholeleg + foot	1,5	0,75
1-2 years		
Face + neck	1,5	0,75
Wholearm + brush	1,5	0,75
Front surface gr. cells + belly	2	1
Back + buttocks	3	1,5
Wholeleg + foot	2	1
3-5 years		
Face + neck	1,5	0,75
Wholearm + brush	2	1
Front surface gr. cells + belly	3	1,5
Back + buttocks	3,5	2
Wholeleg + foot	3	1,5
6-10 years		
Лицо + шея	2	1
Вся рука + кисть	2,5	1,25
Передняя поверхность гр. клетки + живот	3,5	1,75
Спина + ягодицы	5	2,5
Вся нога + ступня	4,5	2,25

Note. FTU - dosage unit, TC - topical glucocorticosteroid.

The anti-inflammatory activity allows MPA to quickly and effectively stop the exacerbation of AD, which has been proven in randomized studies in children and adults. Studies conducted in animals, as well as among healthy volunteers and patients, have demonstrated that the side effects of MPA are lower than in other local TC of the same class of activity.[46, 47].

In a study of 20 healthy volunteers who applied MPA (cream) once a day, there was no thinning of the skin compared to placebo, while betamethasone valerate reduced skin thickness. Systemic side effects may be associated with the absorption of local GCS through the skin, include hyperglycemia, hypertension, leukocytosis, etc. MPA is characterized by a rapid onset of action; its metabolites are inactivated after absorption, and therefore the risk of systemic action in the drug is low. None of the above side effects were detected when using 0.1% MPA ointment for 3 months. Systemic glucocorticosteroids can suppress the function of the hypothalamic-pituitary-adrenal system, in connection with which the question arose about the possible systemic effect of local GCS. On the example of 100 healthy volunteers, no changes in the level of cortisol in blood plasma were observed after 8 days of application of 0.1% MPA (Advantan®) at a dose of 40 g on 60% of the body surface.

In other studies, with pronounced therapeutic effects of MPA (0.1%, Advantan®), no inhibition of the function of the hypothalamic-pituitary-adrenal system was found in the treatment of AD in infants and children with daily application to 5–20% of the body surface for 7 days.

Such high safety and efficacy have been proven exclusively for the original drug, since its basis is patented and included in the master's recipes in Germany.

It should also be noted that the addition of any additional components to the MPA molecule (ceramides, urea) has not been studied from the point of view of local and systemic safety. It is not known how this may affect both the efficiency and the mechanism of bioactivation of the MPA molecule.

Advantan® is available in 4 forms: cream, ointment, oily ointment and emulsion, which, combined with an excellent balance of efficacy and safety, meets the needs of children with AD of various ages. The choice of the dosage form is carried out depending on the stage and manifestations of AD.

Two forms of Advantan deserve special attention, which are most applicable in children's practice: emulsion and cream.

A distinctive feature of the emulsion is the high-water content in the base, due to which it has a cooling, antipruritic effect. In addition, additional components of the base provide a disinfecting effect, dermatoprotective effect and restore the hydrolipid mantle of the skin.

The base of the cream softens the skin and promotes the synthesis of fats in cell membranes.

Considering that the effectiveness of local GC depends on the rate of their penetration into the epidermis and dermis, the rate of penetration of MPA depends both on the dosage form used (cream, emulsion, ointment) and on the lipophilicity of the steroid itself: having a greater affinity for organic substances, accumulates in skin cells in a high concentration and more slowly enters the blood from them (that is, it has a longer local therapeutic effect without giving a systemic side effect).

Numerous comparatives and double-blind, placebo-controlled clinical studies have shown the high efficacy and safety of MPA in children with AD already after 1–4 weeks of using the drug once a day. Comparative studies of topical MPA 0.1% cream, ointment or oily ointment have shown similar efficacy with betamethasone valerate 0.1% and mometazone furoate in similar release forms. Already after 1–3 weeks of treatment, about 90% of children receiving MPA achieved remission or significant improvement in symptoms, complete remission was recorded in 45–65% of patients [25, 46, 51, 52].

In a study involving 221 adult patients with AD, MPA 0.1% cream was applied once a day until control of the disease was achieved. After randomization into groups, patients within 16 weeks. MPA was used 2 times a week together with emollients or only emo tapes. The absence of an exacerbation of the disease was noted in 87.1% of patients in the MPA group, in the group of emollients - in 65.8%. MPA was also more effective than emollients in terms of relapse rate, pruritus intensity and dermatological quality of life index in children. For 16 weeks of proactive MPA therapy, the patients showed no signs of skin atrophy, striae, telangiectasias, irritation or infection. [40].

Thus, the use of desloratadine in the form of a solution or syrup is an effective method of treating AD in children, allowing the majority of patients to achieve remission of the disease. Desloratadine solution is not inferior in effectiveness to the drug in the form of a syrup in the treatment of AD in children and both are well tolerated by patients.

The use of Edem is an effective method of treating atopic dermatitis in children and allows

the majority of patients to achieve remission of the disease. The inclusion of Eden in the form of a syrup in the complex therapy of AD in children in the first years of life ensures the achievement of a rapid clinical effect, primarily by reducing itching, excoriations, erythema and papular elements. Edem syrup is well tolerated by patients.

The pharmacokinetic profile of Advantan, low risk of side effects, and the possibility of a single dose per day make it possible to successfully use this drug for the treatment of AD in children over 4 months of age, as well as in adolescents. Advantan® is available in a variety of forms and has been validated in clinical trials with more than 15,000 patients. The drug has been used for over 20 years, has a unique bioactivation mechanism (proven only in the original drug) and is the optimal therapeutic choice in the treatment of exacerbation of AD in children of any age.

LIST OF REFERENCES:

1. Agafonov A. S. Atopic dermatitis in children and infections complicating the course of the disease/ A. S. Agafonov, V. A. Revyakina// Attending physician. -2011. - No. 1. - p. 8-12.
2. Allergic diseases. Diagnostics and treatment: translated from English: a practical guide / edited by R. Peterson. - M.: GEOTAR-Media, 2000 – - 733 p.
3. Albanova V. I. Non-hormonal external preparations in the treatment of atopic dermatitis in children/ V. I. Albanova// Russian Medical Journal. - 2003. - no. 3. - p. 37-39.
4. Antropov Yu. F. Mental state and neurophysiological features of children with atopic dermatitis / Yu. F. Antropov, V. A. Balabanova// Children's hospital. - 2005. - №2 (20). - Pp. 31-37.
5. Batirov A. R., Zainabitdinova S. N., Yunusov D. M. Experience with the use of syrup of Edem in the treatment of atopic dermatitis in children / Re-health Journal. 2020; No. 2.3: 89-92. DOI: 10.24411/2181-0443/2020-10091.
6. Buryak, V. N., Peshehonova Y. V., Chaban N. And., Dudko, M. V. Skachkova L. P., Bessarab P. A. Experience in optimization of pathogenetic therapy of atopic dermatitis in childhood / Klinichna Pediatrics. 2011; 4 (31): 37-40.
7. Ganiev A. G., Nazarov K. D. Modern complex treatment of the infant form of atopic dermatitis in children. "Doktoraxborotnomasi" / / Bulletin of the doctor/ Quarterly scientific and practical journal No. 3, 015, pp. 76-79.
8. Ganiev A. G., Temirova O. Kh. Algorithm of basic skin care in atopic dermatitis in children/ "re-healthjournal" //Andijan 0 0. Scientific and practical journal. Release: 1. St: 98-306.
9. Geppe N. A., Seliverstova N. A., and Yutusheva M. G. Efficacy of desloratadine in atopic dermatitis in children. Allergology. 2005; 2: 9-11.
10. Grigoryan N. S. Modern pathogenetic approaches to the treatment of atopic dermatitis/ / N. S. Grigoryan, N. S. Kochergin, I. V. Kosheleva// Practical medicine. - 2011. - №2 (49). - P. 31-35.
11. Dergach V. V. Immunotropic therapy in atopic dermatitis in children: a comparative analysis of clinical and immunological effectiveness/ V. V. Dergach/ / Russian Journal of Skin and Venereal diseases. - 2007. - No. 2.-p. 27-30.
12. Katina M. M. Complicated forms of atopic dermatitis in children: clinical and immunological features/ M. M. Katina, E. A. Potrokhova, O. V. Antonov / / Pediatrics. - 2010. - Vol. 89. - No. 4. - p. 32-35.Коростовцев Д. С. Дезлоратадин (Эриус) — новый неседативный антигистаминный препарат (высокоселективный антагонист Н1-рецепторов). Аллергология. 2002; 1: 44–50.
13. Korostovtsev D. S., Makarova I. V., Revyakina V. A., Gorlanov I. A. SCORAD index-an objective and standardized method for assessing skin lesions in atopic dermatitis. - 2010. - No. 3. - pp. 39-45.
14. Kungurov N. V., Kohan M. M., Keniksfest Yu. V., Grishaeva E. V., Khoseva E. N. The use of the antihistamine drug Erius (desloratadine) in the complex therapy of chronic dermatoses. Allergology. 2005; 3: 51-55.
15. Makarova I. V. Atopic dermatitis in children. Pos. for practice. doctors. St. Petersburg. 2003. 54 p.
16. Makarova I. V., Trusova O. V., Zhiglinskaya O. V., Medvedeva E. A., Galenko L. A. Comparison of the effectiveness and tolerability of the use of desloratadine preparations (solution and syrup) in the treatment of atopic dermatitis in young children. Questions of modern pediatrics. 2015; 14 (2): 287–291. doi: 10.15690/vsp.v14i2.1300. Scientific and

practical program "Atopic dermatitis in children: diagnosis, treatment and prevention". M. 2000. 98 p.
17. Nedelskaya S. N. Allergy and antihistamines / S. N. Nedelskaya, T. G. Bessikalo / / News of medicine and pharmacy. - 2007. - No. 8. - p. 3-4.
18. Pytsky V. I. Allergic diseases / V. I. Pytsky, N. V. Adrianova, A.V. Artomasova. - M.: Triada-X, 1999 — - 470 p.
19. Revyakina V. A., Taganov A. V. Kuvshinova E. D. Atopic dermatitis, modern strategy in therapy // Attending physician. – 2019. - No. 5.
20. Smirnov G. I. Allergic dermatoses in children. - M.: BEECH, Ltd., 1998. -300 C.;
21. Smirnov G. I. Place of topical corticosteroids in the treatment of atopic dermatitis in children // Practice of a pediatrician. - 2006. - No. 1. - p. 10-16.
22. Agrawal D. K. Pharmacology and clinical efficacy of desloratadine as an anti-allergic and anti-inflammatory drug. Exp. Opin. Investig. Drugs. 2001; 10 (3): 547–560.
23. Baranov A.A., Namazova-Baranova L.S. Atopic dermatitis in children. Clinical guidelines for pediatricians. Moscow: Pediatr = Pediatrician; 2017. 74 p. (In Russ.).
24. Billich A., Aschauer H., Aszodi A., Stuetz A. Percutaneous absorption of drug used in atopic eczema: pimecrolimus permeates less through skin than corticosteroids and tacrolimus // Int. J. Pharmaceutics. - 2004. - V. 269. - P. 29–35.
25. Canonica G. W., Blaiss M. Antihistaminic, anti-Inflammatory, and antiallergic properties of the nonsedating second-generation antihistamine desloratadine: a review of the evidence. WorldAllergyOrgan. J. 2011; 4 (2): 47–53.
26. Chamlin S.L., Kao J., Frieden I.J. et al. Ceramide dominant barrier repair lipids alleviate childhood atopic dermatitis: changes in barrier function provide a sensitive indicator of disease activity // J. Am. Acad. Dermatol. - 2002. - V. 47. -P. 198–208.
27. Cork M. Limitations of current therapy in atopic eczema // Controlling atopic eczema: Satellite Symposium. Abstracts. - Florence, 2014. - P. 6–7.
28. Eichenfield L.F., Tom W.L., Berger T.G., Krol A., Paller A.S., Schwarzenberger K., et al. Guidelines of care for the management of atopic dermatitis. Section 2. Management and treatment of atopic dermatitis with topical therapies. J Am Acad Dermatol. 2014;71(1):116– 132. doi: 10.1016/j.jaad.2014.03.023.
29. Galli E., Cicconi R., Rossi P. et al. Atopic dermatitis: molecular mechanism, clinical aspects and new therapeutical approaches // Curr. Mol. Med. - 2013. V. 111, № 5. - P. 127–138.
30. Ganiev A. G., Xudayberganov M. R. Immunological mechanisms of development of complicated forms of atopic dermatitis/American Journal of Medicine and Medical // Sciences Vol. 10 No. 6, 2020, pp. 397-399.
31. Hanifin J.M. Epidemiology of atopic dermatitis // Immunol. Allergy Clin. NA. - 2002. - V. 22. - P. 1–24.
32. Harper J., Lakhanpaul M., Wahn U. et al. Pimecrolimus (Elidel®, SDZ ASM 981) cream 1% blood levels are consistently low in children with extensive atopic eczema // JEADV. - 2011. - V. 15 (Suppl. 2). - P. 109.
33. Hoare C., Li Nan POA., Nilliams H. Systematic review of treatment for atopic eczema // Health. Technol. Assess. — 2000. — № 7. — R 25-180.
34. Hoetzenecker W., Ecker R., Kopp T. et al. Pimecrolimus leads to an apoptosis induced depletion of T cells but not Langerhans cells in patients with atopic dermatitis // J. Allergy Clin. Immunol. - 2005. - V. 115. - P. 1276–1283.
35. Hultsch T., Kapp A., Spergel J. Immunomodulation and safety of topical calcineurin inhibitors for the treatment of atopic dermatitis // Dermatology. - 2005. - V. 211. - P. 174–187.
36. Joo Sh., Kau A.L. (eds.). Allergy, Asthma, and Immunology Subspecialty Consult. The Washington Manual. Second Edition. Washington University School of Medicine; 2013. 205 c. Available at: https://www.worldcat. org/title/washington-manual-allergy-asthmaand-immunology-subspecialty-consult/ oclc/713189757.
37. Kapp A., Papp K., Bingham A. et al. Longterm management of atopic dermatitis in infants with topical pimecrolimus, a nonsteroid antiinflammatory drug // J. Allergy Clin. Immunol. - 2002. - V. 110. - P. 277–284.
38. Kliegman R.M., St. Geme J.W. III, Blum N.J., Shah S.S., Behrman R.E. Nelson textbook of pediatrics. 21 Edition. Philadelphia, PA: Elsevier; 2019:5006-5032. Available at: https://www.

worldcat.org/title/nelson-textbook-of-pediatrics/oclc/1096283151.
39. Korotkiy N.G., Taganov A.V., Shimanovskiy N.L. Therapeutic experience in using Advantan to treat atopic dermatitis in children. Pediatriya = Pediatria. 2000;79(5):18. (In Russ.) Available at: https://cyberleninka.ru/article/n/opyt-primeneniya-advantana-metilprednizolona-atseponata-v-detskoy-dermatologicheskoy-praktikepri-lechenii-atopicheskogo-dermatita.
40. Lakhanpaul M., Davies T., Allen B. et al. Pimecrolimus (SDZ ASM 981) cream 1%: Minimal systemic absorption in infants with atopic dermatitis during longterm treatment // Ann. Dermatol. Venerol. - 2012. - V. 129. - P. 415
41. Leung D.Y., Boguniewicz M., Howell M.D. et al. New insights into atopic dermatitis // J. Clin. Invest. - 2014. - V. 113. - P. 651–657.
42. Levina Y.G., Alekseeva A.A., Vishneva E.A., Efendieva K.E., Tomilova A.Y. Peculiarities of external therapy of atopic dermatitis in children: role of methylprednisolone aceponate. Pediatričeskaâfarmakologiâ = Pediatric pharmacology. 2014;11(5):52-58. (In Russ.) doi: 10.15690/pf.v11i5.1165.
43. Luger T.A. Balancing efficacy and safety in the management of atopic dermatitis: the role of methylprednisolone aceponate. J Eur Acad Dermatol Venereol. 2011;25(3):251–258. doi: 10.1111/j.1468-3083.2010.03789.x.
44. Mahmoudi M. (ed.). Allergy and Asthma: The Basics to Best Practices. Springer; 2019:190-210. Available at: https://www.springer.com/gp/book/9783030051464.
45. Namazova-Baranova L.S., Gankovskaya L.V., MeshkovaR.Ya. Fundamentals of Clinical Immunology and Allergology. Moscow: Pediatr = Pediatrician, 2016. 152 p. (In Russ.).
46. Niedner R., Zaumseil R.-P. Advantan® milk/ cream/ointment in children with atopic eczema and other dermatoses – an observational study in 558 children. (In German). Akt Dermatol. 2004;30(6):200–203. doi: 10.1055/s-2004-814472.
47. Piteau Sh. (ed.). Update in Pediatrics. Springer; 2018:39-59. Available at: https://www.springer.com/gp/book/9783319580265#aboutBook.
48. Potenzieri C., Undem B. J. Basic Mechanisms of Itch. Clin. Exp. Allergy. 2012; 42 (1): 8–19.
49. Romanyuk F.P., Alferov V.P. Clinic manifestation and treatment of atopic dermatitis: a guide for doctors. St. Petersburg: Asterion, 2014. 78 p. (In Russ.).
50. Schneider L., Tilles S., Lio P., Boguniewicz M., Beck L., Lebovidge J., Novak N., Bernstein D., Blessing-Moore J., Khan D., Lang D., Nicklas R., Oppenheimer J., Portnoy J., Randolph C., Schuller D., Spector S., Wallace D. Atopic dermatitis: a practice parameter update 2012. J Allergy Clin Immunol. 2013;(131):295–299. e1-27. doi: 10.1016/j.jaci.2012.12.672.
51. Silverberg J.I., Nelson D.B., Yosipovitch G. Addressing treatment challenges in atopic dermatitis with novel topical therapies. J Dermatolog Treat. 2016;27(6):568-576. doi: 10.1080/09546634.2016.1174765.
52. Spergel J.M., Paller A.S. Atopic dermatitis and the atopic march // J. Allergy Clin. Immunol. - 2003. - V. 112 (6 Suppl.). - P. 118–127.
53. Torrelo A. Methylprednisolone aceponate for atopic dermatitis. Int J Dermatol. 2017;56(6):691–697. doi: 10.1111/ijd.13485.
54. Wahn U., Bos J.D., Goodfield M. et al. Efficacy and safety of pimecrolimus cream in the longterm management of atopic dermatitis in children // Pediatrics. - 2012. - V. 110. - P. 1–8.
55. Wellington K., Noble S. Pimecrolimus. A review of its use in atopic dermatitis // Am. J. Clin. Dermatol. - 2014. - V. 5, № 6. - P. 479–495.
56. Wuthrich B. Clinical aspects, epidemiology, and prognosis of atopic dermatitis // Ann. Allergy Asthma Immunol. - 1999. - V. 83. - P. 464–470.
57. Zuberbier T., Chong S.U., Grunow K. et al. The ascomycin macrolactam pimecrolimus (Elidel, SDZ ASM 981) is a potent inhibitor of mediator release from human dermal mast cells and peripheral blood basophils // J. Allergy Clin. Immunol. - 2001. - V. 108. - P. 275–280.

Entered 09.01. 2021