

**Yu.G. Levina<sup>1, 2</sup>, L.S. Namazova-Baranova<sup>1, 2, 3</sup>, A.A. Alexeeva<sup>1, 2</sup>, E.A. Vishneva<sup>1</sup>, K.E. Efendieva<sup>1, 2</sup>, A.Yu. Tomilova<sup>1, 2</sup>**

<sup>1</sup>Scientific Center of Children's Health, Moscow, Russian Federation

<sup>2</sup>Sechenov First Moscow State Medical University, Russian Federation

<sup>3</sup>Pirogov Russian National Research Medical University, Moscow

## **Clinical and pharmacological peculiarities of cetirizine use for the therapy of allergic diseases in children**

### **Author affiliation:**

*Levina Yuliya Grigor'evna*, MD, head of the department of standardization and clinical pharmacology, assistant professor at the department of allergology and clinical immunology of the pediatric faculty of I.M. Sechenov First Moscow State Medical University

**Address:** bld. 1, 2, Lomonosovskii Ave., Moscow, 119991.

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*The review is dedicated to treatment of allergic diseases in children, particularly to the use of the 2nd generation antihistamine. It demonstrates that mediator histamine has the crucial role in pathophysiology of the allergic reaction. Antihistamines block histamine action aimed at H1 receptors by way of competitive inhibition. The 2nd generation antihistamines are the drugs of choice for the treatment of allergic diseases due to the absence of sedative effect. The review presents clinical and pharmacological description of the selective 2nd generation antihistamine cetirizine, efficacy and safety of which have been appraised in numerous long-term clinical studies in children with allergic rhinitis, urticaria and atopic dermatitis.*

**Keywords:** antihistamines, cetirizine, children, allergic rhinitis, atopic dermatitis.

The prevalence of allergic diseases such as seasonal and persistent allergic rhinitis, urticaria, atopic dermatitis and bronchial asthma has been steadily increasing in recent years. Allergic diseases have a tremendous impact on the quality of patients' life.

Common pathogenetic link of development of any form of allergy (true and pseudoallergic) is the release of biologically active substances which leads to the development of one or another symptom complex (depending on the "shock" organ).

The most important role in the pathophysiology of allergic diseases belongs to histamine mediator (5[2-aminoethyl]-imidazole) which is primarily contained in mast cells and basophils. The influence of histamine released from the IgE-activated mast cells during the early phase of an allergic reaction on organs and tissues mainly determines acute symptoms of allergic diseases. As a result of development of type I allergic reaction and the IgE-dependent degranulation of mast cells, the elevation of histamine concentration in blood plasma and tissue fluid takes place. The histamine level increase may also be caused by other mechanisms of cell activation: e.g., in the event of pseudoallergic reactions, the mast cell membrane is destroyed not by an antigen-antibody complex, but by some chemical or other agent.

Pharmacological action of histamine is mediated through the stimulation of histamine receptors. Currently, four types of histamine receptors are known. Development of allergic reactions is mainly associated with the H1-histamine receptors, the activation of which leads to the contracture of smooth muscles of bronchi and gastrointestinal tract, increased vascular permeability, increased mucus secretion by nasal mucous glands and irritation of nerve endings. Histamine impact on histamine receptors results in the involvement of respiratory tract mucosae in the pathological process and occurrence of symptoms of allergic rhinitis and bronchial asthma, namely, itching, sneezing, swelling of mucosae, mucus hypersecretion and bronchospasm; when the ocular mucosa is affected, symptoms of allergic conjunctivitis take place, namely, itching, redness, swelling, lacrimation. The typical clinical effects of histamine on the skin are itching,

hyperemia and formation of blisters; the typical clinical effects of histamine on the gastrointestinal tract are abdominal pains, emesis, diarrhea, increased production of hydrochloric acid and pepsin in the stomach and increased mucus production. The impact on cardiovascular system is represented by decrease in blood pressure and heart rhythm disturbances. Reduction of exposure to an allergen is the first necessary step in the treatment of allergic diseases [1, 2].

Blockers of histamine H1-receptors alleviate the histamine-induced hypotension and spasms of smooth muscles (bronchi, intestinal tract), reduce capillary permeability, prevent development of histamine swelling, reduce hyperemia and itching and thus alleviate and prevent development of allergic reactions.

The first substances with antihistamine activity were created in 1936 (D. Bovet, A. Staub). The first antihistamine used on humans was synthesized in 1942. In 1960s, the heterogeneity of body receptors to histamine was proved; three subtypes of histamine (H1, H2 and H3) were distinguished. They differ in structure, localization and physiological effects occurring in the event of activation/blockade thereof. The active period of synthesizing and clinically testing various antihistamines has been ongoing since then. The majority of the used antihistamines have a number of specific pharmacological effects which distinguish them into a separate group: antipruritic, decongestant, antispasmodic, anticholinergic, antiserotonin, sedative and topical anesthetic; they also prevent histamine-induced bronchospasm. Certain properties of medications are determined not by the histamine blockade, but by structural peculiarities: they block the action of histamine on H1-receptors by means of competitive inhibition, and their relation to these receptors is considerably lower than the one of histamine. These medications are not capable of displacing receptor-bound histamine; they only block the unoccupied or released receptors. Therefore, H1-blockers are most effective for prevention of immediate allergic reactions; in the event of enhanced reaction, they block release of new portions of histamine. Chemically, most of them belong to fat-soluble amines, as they have a similar structure. The nucleus is represented by an aromatic and/or heterocyclic group and is bound with an amino group by means of a nitrogen, oxygen or carbon molecule. The nucleus determines severity of antihistamine activity and some of the properties. Knowing its composition, the strength of the medication and its effects may be predicted, e.g., its ability to penetrate the blood-brain barrier [3].

According to one of the most popular classifications, antihistamines are divided into the 1<sup>st</sup> and the 2<sup>nd</sup> generation medications (according to the time of creation). 1<sup>st</sup> generation medications are also called sedatives (on the basis of the dominant side effect) in contrast to the non-sedative 2<sup>nd</sup> generation medications (pic.).

**1<sup>st</sup> generation antihistamines** have never been adequately clinically tested for children; however, they are often prescribed to patients of that age group. They block H1-receptors only by 30%; thus, prescription of large doses of medication is required to achieve the desired antihistaminic effect. These drugs have a pronounced sedative effect, since they easily penetrate the blood-brain barrier due to their high lipophilicity and cause blockade of H1- and M-receptors of the central nervous system; this results in aggravation of apathy, drowsiness and attention concentration of the patients. Long-term regular intake of the aforementioned medications may contribute to cognitive deterioration of children. In addition, these medications are not recommended for children with bronchial asthma and allergic rhinitis due to the M-cholinolytic (atropine-like) effect. According to the US poison control services, the 1<sup>st</sup> generation antihistamines are the cause of death of adults of overdose poisoning in 8.3% of the cases. Some studies indicate that diphenhydramine and other 1<sup>st</sup> generation medications (dextromethorphan, doxylamine, chlorpheniramine, etc.) which are commonly used in the United States, have been revealed in the children, primarily under 12 years of age, who died of various causes, which may have been related to the 1<sup>st</sup> generation antihistamine overdose [1, 4].

**2<sup>nd</sup> generation antihistamines** have been well studied and undergone multiple clinical tests on children, which have confirmed their effectiveness and safety. The medications have high specificity to H1-receptors and do not possess the M-cholinolytic effect. Their advantage lies in the absence of the sedative effect and the absence of influence on the cognitive function, as well

as in the possibility of long-term intake. This is the treatment of choice for allergic diseases. The essential distinction of the 2<sup>nd</sup> generation antihistamines is that they not only have a selective H<sub>1</sub>-blocking action, but also an anti-inflammatory effect [1, 2, 5, 6].

Cetirizine (created in 1987) is one of the most frequently prescribed 2<sup>nd</sup> generation antihistamines in pediatric practice. The original medication of cetirizine is Zyrtec (USB, Belgium). In contrast to generic drugs, it contains no stain in coated pills and corn starch as filler (hence, it can be prescribed in case of an allergy to gramineae). Shelf life of the original medication is 5 years, of the generic medication – not more than 2-3 years.

Characteristics of pharmacokinetics and pharmacodynamics of the medication determine its effectiveness and, partially, safety, hence, they may differ depending on the age group.

## **PHARMACOLOGICAL CHARACTERISTICS OF CETIRIZINE**

Cetirizine ([2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy] acetic acid) is a carboxylated metabolite of hydroxyzine (representative of the 1<sup>st</sup> generation of antihistamines) and exists as a zwitterion (bipolar ion); this partially explains its limited biotransformation, low or moderate lipophilicity and, consequently, a limited ability to penetrate the blood-brain barrier and produce an effect on the central histamine receptors. That is precisely why cetirizine has a less undesirable side effect (sedation) than the 1<sup>st</sup> generation antihistamines, including hydroxyzine. It is a highly selective antagonist of H<sub>1</sub>-receptors with very low affinity to receptors of other types such as serotonin (5-HT<sub>2</sub>), dopamine (D<sub>2</sub>), M-cholinolytic receptors and  $\alpha$ <sub>1</sub>-adrenoceptors, therefore, it has neither side effects associated with interaction with the aforementioned types of receptors nor side effects of the 1<sup>st</sup> generation H<sub>1</sub>-antihistamines. Cetirizine is one of the few antihistamines excreted with urine without being metabolized by the system of cytochromes P-450 of the liver and has a low potential of interaction with other drugs [7].

## **PHARMOKOKINETICS**

Cetirizine is a long-acting drug with a rapid onset of action. Therapeutic effect of cetirizine is apparent after a single intake of a single dose (after 20 minutes – in 50% of the patients, after 1 hour - in 95% of the patients) and lasts for 24 hours. In the observed children aged from 5 to 12 years, the peaks of plasma concentration reached 427 and 978 mg/l after a single intake of cetirizine in doses of 5 or 10 mg, respectively. The period of half-excretion of the medication from blood did not depend on the dose and took 7 hours. Up to 40% of the drug is excreted unchanged with urine within 24 hours. At an earlier age (2-4 years), the cetirizine half-excretion period after a single dose of 5 mg (0.3 mg/kg of body weight) took 4.9 hours; in neonates - 2.4 hours. Although these figures are slightly smaller in children than in adults, the differences are not that significant, therefore, there is no need to change the frequency of intake [8].

Cetirizine remains the reference drug of antihistamine and anti-allergic action used for comparison in the process of development of new antihistamines and anti-allergic agents. Characteristics of the antihistamine activity of clinical relevance are based on the ability of antihistamines to relieve peripheral effects of histamine in those very tissues, which are primarily involved in the clinical manifestations of the allergy [8]. Antihistamine effect of cetirizine develops rapidly. A single dose of 10 mg of the medication inhibits the histamine-induced blistering-hyperemic skin reaction as effectively as loratadine and more effectively than fexofenadine in therapeutic doses [9, 10]. The antihistamine action of cetirizine is demonstrated in other tissues involved in allergic reactions as well. Intake of 10 mg of cetirizine BID inhibits such histamine-induced reaction of the nasal mucosa as sneezing and congestion in both virtually healthy donors and allergic patients. Cetirizine also provides a dose-dependent (5, 10 and 20 mg) inhibition of histamine-induced bronchospasm in virtually healthy persons [8].

Clinical studies of children demonstrated that cetirizine also possesses anti-inflammatory activity; it reduces production of leukotrienes *in vitro* [7, 11]. Effect of the leukotriene level decrease is caused by the decreased migration of leukotriene-producing cells (eosinophils, basophils, and macrophages) towards the allergic response site [12]. Cetirizine decreases production of nitric oxide (NO), inhibits expression of the Inter-Cellular Adhesion Molecule 1 (ICAM-1) on epithelial cells and reduces formation of the inflammatory cell infiltrate. It also induces a switch of Th1/Th2 balance towards the Th1-response. In children with allergic rhinitis and increased sensitivity to house dust mites, the standard treatment with cetirizine (28 days) would lead to reconstruction of the ability of peripheral blood mononuclear cells to produce cytokines in response to *in vitro* stimulation with mite allergens. After a course of treatment, we observed the increase in the production of interleukin (IL) 10 and interferon- $\gamma$ . The production of IL 4 would not change, although the interferon- $\gamma$ /IL 4 ratio would increase; this corresponds to a switch of cytokine profile Th1/Th2 towards Th1-response and reconstruction of the immune response. However, clinical significance of this phenomenon is difficult to estimate even if it is confirmed [7, 8, 13, 14]. Thus, anti-allergic effect of cetirizine is complex: the blocking effect towards peripheral H1-receptors, decreased sensitivity of tissues to other intermediaries of the immediate phase of the allergic response and inhibition of involvement of eosinophils and other cells; this expands pharmacological action of cetirizine to both early and late stages of allergic response [8].

### **SAFETY, ACCEPTABILITY AND SIDE EFFECTS**

High safety of the medication proven by numerous clinical studies is particularly important for pediatric practice. Placebo-controlled studies of children aged from 6 months to 11 years of age demonstrated that 2.5-10 mg of cetirizine a day were well accepted [15]; the most frequently reported adverse events were headache (11-14%), pharyngitis (3-6%), aggravated cough (3-4%), drowsiness (2-4%), and abdominal pain (4-6%). Adverse events occurred more frequently after intake of cetirizine in the children aged 2-11 year than in the placebo group. The cetirizine acceptability profile in the children aged 6-24 months did not differ from the one in the placebo group. Cases of drowsiness in placebo-controlled studies of children aged 2-11 years depended on the dose of the medication. The level of drowsiness of infants aged 6-24 months did not differ between the cetirizine group and the placebo group. The level of drowsiness in the group of adolescents taking cetirizine was significantly lower than in the group treated with hydroxyzine and was virtually the same as the one observed when other 2<sup>nd</sup> generation antihistamines are used. Nevertheless, its sedative effect was more significant than the sedative effect of fexofenadine in several clinical studies and of loratadine or fexofenadine in postmarketing studies [7]. According to the Food and Drug Administration (FDA), cetirizine causes drowsiness in 1.9-4.2% of cases; this indicates a very low degree of penetration into the blood-brain barrier. International observational study (OSCAR) was aimed at analysing satisfaction of patients (children with allergic rhinitis aged 2-12 years) and doctors with effectiveness and acceptability of various antihistamines. Out of the 2<sup>nd</sup> generation antihistamines, drowsiness was most frequently reported in the cetirizine group [16].

A randomized double-blind placebo-controlled study of 600 children with atopic dermatitis at the age of 12-24 months demonstrated that the intake of 0.25 mg/kg of cetirizine BID over a period of 18 months did not affect behavior and cognitive function both during the study and in the follow-up period [17].

A large multicenter study conducted by the Early Treatment of the Atopic Child (ETAC) estimated the safety of long-term intake of cetirizine drops (10 mg/ml) by children aged 12-24 months over an 18-month long treatment and 18-month-long follow-up period. Doses of cetirizine prescribed in the study ranged from 4 mg for 7.5 kg children to 11 mg for 24.5 kg children. The frequency of adverse events was the same as in the placebo group; no tachyphylaxis was observed [18]. Furthermore, cetirizine has no cardiotoxic effect; it does not

extend the QT and QT(c) intervals [18-20]. Zyrtec is the only 2<sup>nd</sup> generation medication approved for use in the Russian Federation from the age of 6 months, whereas the minimum age for prescribing other 2<sup>nd</sup> generation antihistamines is 2 years. It is important for pediatric practice that the medication has a unique dosage form (drops) for children, which, unlike syrups, is sugar-free and contains no flavorings.

## POSOLOGY AND ADMINISTRATION

Oral intake. For children aged from 6 to 12 months the intake is 2.5 mg (5 drops) OD. For children aged from 1 to 2 years the intake is 2.5 mg (5 drops) OD-BID. For children aged from 2 to 6 years the intake is 2.5 mg (5 drops) BID or 5 mg (10 drops) OD.

For adults and children over 6 years of age the daily dose is 10 mg (1 tablet or 20 drops). For adults the intake is 10 mg OD; for children the intake is 5 mg BID or 10 mg OD. Sometimes the initial dose of 5 mg may be sufficient to achieve therapeutic effect.

For patients with renal failure, the dose is reduced depending on creatinine clearance: at 30-49 ml/min the intake is 5 mg OD; at 10-29 ml/min the intake is 5 mg every two days.

## THERAPEUTIC EFFECTIVENESS

Therapeutic effectiveness of cetirizine was evaluated in clinical studies of patients with various allergic diseases.

**Allergic rhinitis (AR)** is an IgE-associated inflammatory disease of the nasal mucosa, which manifests itself with a complex of such symptoms as sneezing, itching, rhinorrhea and nasal congestion. In the event of seasonal AR, symptoms occur during the flowering period (trees and grass) of the plants producing causal allergens. Persistent AR usually develops in the event of sensitization to household allergens (house dust mites, cockroaches, pet dander). Systemic non-sedative 2<sup>nd</sup> generation antihistamines, which do not interact with cytochrome P-450 and do not produce sedative effect are recommended for treating allergic rhinitis and conjunctivitis both in children and adults. The 2<sup>nd</sup> generation antihistamines constitute the baseline therapy of AR regardless of its severity due to the fact that AR is a systemic disease, which is often associated with other manifestations of allergy – bronchial asthma / bronchial hyperreactivity, urticaria and atopic dermatitis. In addition, clinical studies have demonstrated that monotherapy with intranasal corticosteroids is not always sufficiently effective in the event of moderate and severe forms of the disease (more than 50% of the patients require supplemental prescription of antihistamines). Combined therapy with the 2<sup>nd</sup> generation antihistamines and inhaled corticosteroids contributes to the effectiveness of treatment when low doses of steroids are used [21, 22]. Antihistamine medications are effective against the symptoms of allergic rhinitis associated with the action of histamine, such as itching, sneezing, rhinorrhea and ocular symptoms, but are less effective against nasal obstruction [1, 23, 24].

In children aged 2-6 [25], 6-11 [26, 27] or 6-12 [28] years with seasonal allergic rhinitis, effectiveness of 5-10 mg of cetirizine per day was evaluated in several randomized double-blind multicenter studies in parallel groups over the period of 2-4 weeks. Cetirizine was significantly more effective than placebo [25-28] and loratadine [27] for reducing the symptoms associated with seasonal allergic rhinitis. There is evidence that long-term cetirizine treatment helps to achieve a more effective control over inflammation and clinical symptoms in patients with allergic rhinitis compared with on-demand therapy [28, 29]. Cyprandi et al. [30] demonstrated that children who were taking 5 mg of cetirizine per day over the period of 4 weeks during the flowering period featured a significant decrease in clinical symptoms accompanied by the decreased expression of ICAM-1 on epithelial cells ( $p < 0.05$ ), soluble ICAM-1 ( $p < 0.05$ ) and eosinophil cationic protein ( $p < 0.05$ ) in nasal lavage (in comparison with placebo). Moreover, there was a significant correlation between the decrease in symptoms, cellular infiltration and ICAM-1 expression. Another study of the effect of cetirizine treatment (5 mg per day over the

period of 2 weeks) on inflammation of the nasal mucosa in children with persistent allergic rhinitis demonstrated a significant decrease in the level of IL 4 ( $p < 0.01$ ), IL 8 ( $p = 0.01$ ) and ICAM-1 expression on epithelial cells ( $p < 0.02$ ) (in comparison with placebo) [31, 32]. Prescription of cetirizine improves the HR-QOL quality of life indicator in the children aged 6-11 years with seasonal allergic rhinitis evaluated using the PRQLQ questionnaire. The aforementioned figures correlate with the improvement of the total symptoms score [33].

In large-scale randomized studies of children with persistent allergic rhinitis aged 2-14 years given 2.5-10 mg of cetirizine per day demonstrated significantly higher effectiveness thereof for reducing the total symptom score (TSS) than placebo [34], as well as according to a global assessment of effectiveness by researchers [34-37]. Global assessment of the effectiveness by researchers was the same for cetirizine and loratadine, which were prescribed at 0.2 mg/kg per day over the period of 4 weeks [38]; however, according to the daily appraisal of the patients, such symptoms as rhinorrhea, sneezing, nasal congestion and nasal itching were more effectively inhibited by cetirizine ( $p < 0.001$ ) [38]. 0.15 mg/kg of cetirizine per day were effective for the treatment of allergic rhinitis-associated cough, as demonstrated by a 4-week-long randomized double-blind placebo-controlled study of parallel groups of 20 children aged 6-15 years. Frequency and intensity of cough significantly decreased in patients treated with cetirizine (compared with the placebo group [ $p < 0.05$ ]). No changes in respiratory function (PEF and FEV1) were observed [30].

**Atopic dermatitis** is a chronic allergic inflammatory skin disease accompanied by itching, rashes (defined by age-adequate morphology) and staging. Out of all allergic diseases, atopic dermatitis is the earliest and the most frequent manifestation of utopia; it is diagnosed in 80-85% of infants with allergies. In the event of atopic dermatitis, antihistamines should be used as the means of combating itching – one of the pathogenetic mechanisms supporting inflammation [1]. Placebo-controlled studies of the antipruritic effect of oral antihistamines have demonstrated disputable results: some of these effects were identical placebo effects, while several other studied demonstrated a good antipruritic effect [39-41].

According to the EAACI/AAAAI/PRACTALL report, the main effect of antihistamines in the event of atopic dermatitis is associated with their sedative effect, which is why more modern drugs of this group (with minimum sedation) have low clinical effectiveness [42].

A double-blind placebo-controlled ETAC study analyzed intake of 0.25 mg/kg of Zyrtec BID over the period of 18 months by 817 infants with atopic dermatitis at the age of 12-24 months. Severity of symptoms of atopic dermatitis equally decreased by the end of the study in the patients treated with cetirizine (SCORAD index decreased from 24.9 to 15.2;  $p < 0.001$ ) and in the placebo group (from 25.1 to 15.7;  $p < 0.001$ ). Use of cetirizine allowed patients with atopic dermatitis to reduce the need in external corticosteroids. Weak topical corticosteroids (class 1) were prescribed for the equal number of days in the placebo group and for the patients treated with cetirizine (21 and 25% of the days, respectively). However, medium and strong corticosteroids were used less often in the cetirizine group than in the placebo group (19 and 25% of the days, respectively;  $p = 0.067$ ). The corticosteroid-saving effect was significantly greater in the subgroup of infants with severer atopic dermatitis at the beginning of the study (SCORAD index  $\geq 25$ ; 26 and 35% of the days, respectively;  $p = 0.014$ ) [43]. Similar results were obtained in an 8-week-long placebo-controlled study of 22 patients aged 6-12 years, who were taking 5 or 10 mg of cetirizine OD. Concomitant therapy was required less frequently in the cetirizine group than in the placebo group (18 and 82%, respectively;  $p < 0.01$ ) [44]. The results obtained in the ETAC study and the 6-month follow-up period showed a decrease of the risk of progression of atopic march (subsequent development of asthma) by 40-50% in children with allergy to grass pollen and house dust mites. No adverse effects on behavior and psychomotor function were observed throughout the entire long cetirizine treatment period (children from 1 to 2 years of age with a daily dose of 0.25 mg/kg BID). The following publications have questioned the ETAC conclusions due to diversity of groups; therefore, a new clinical trial (EPAAC) was carried out. In that study, levocetirizine (Ksizal) was given to 510 young children with atopic

dermatitis (follow-up period – 18 months). Levocetirizine demonstrated the ability to prevent development of urticaria in children with atopic dermatitis [1]. Cetirizine was also effective in the children aged 12-24 months regarding prevention of the symptoms of acute urticaria. The study demonstrated that acute urticaria occurred far less frequently in the children given 0.25 mg/kg of cetirizine BID than in the children taking placebo over the period of the 18-month-long treatment (6 and 16%, respectively;  $p < 0.001$ ) [45]. No differences in the incidence of acute urticaria between groups were observed throughout the 6-month-long follow-up period after treatment withdrawal. Results of a double-blind placebo-controlled randomized study of children with sensitization to house dust mites demonstrated that long-term therapy (3 years) employing cetirizine in the daily dosage (OD) may reduce the risk of sensitization spectrum expansion in children with a monovalent allergy [46].

Thus, such pharmacological characteristics of cetirizine as rapid onset and duration of action, high specificity to H1-receptors, impact not only on the early, but also on the late stage of immediate allergic reactions, effectiveness, safety, possibility of long-term use confirmed by numerous clinical studies and the availability of a convenient dosage form (drops) permitted for infant intake (from 6 months of age) make it a suitable medication for the treatment and prevention of a variety of infant allergic diseases.

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# **Pucture.**

