State Scientific Centre of Russian federation
Immunological Institute of Russian Federation Health Resort

CLINICAL ASPECTS OF USE OF IMMUNOMODULATOR POLYOXIDONIUM

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INTRODUCTION

Constant growth of sickness rate, growth of pathological cases, inclination towards chronicity of processes, formation of polyresistance on drug specimens can be evaluated as an evidence of immune system weakening.

Therefore it is difficult to overcome infectious diseases without rectification of immunodeficiency by means of relevant immunotropic preparations. It is evident that treatment of chronic infectious inflammatory processes has to be complex consisting of ethiotropic chemical therapeutic preparations directed at elimination of originator and immunomodulating preparations effecting normalization of functional activity of immune system.

One of the preparations for treatment and prophylaxis of diseases connected with damage of immune system is Polyoxidonium – a macromolecular compound with high immunomodulating activity.

Polyoxidonium is registered in Russian Federation from the year 1996, under registration number 96/302/9, FS 42-3906-00. Several years of experience with Polyoxidonium demonstrate its high clinical efficiency in the complex treatment of chronic recurring, torpid infectious inflammatory processes (of skin, soft tissues, eyes, bronchial pulmonary apparatus, intestinal and urogenital tract), which are on the background of primary or secondary immunodeficiencies.

Polyoxidonium is a copolymer N-oxi 1,4-ethylenpiperazine and (N-carboxiethyl) – 1,4 piperazine bromide with molecular weight 100 KD. This preparation belongs to the class of water-soluble derivates of hetero-chain aliphatic polyamines. This class of compounds has no parallel in the world concerning its structure and its characteristics.

Polyoxidonium was obtained and examined fully in the State Scientific Centre – Immunologic Institute of RF HR. Immapharma, ltd., Moscow, Russia produces this preparation. Clinical studies were carried out by 10 medical institutions of Moscow, under the management of State Scientific Institute – Immunologic Institute of RF HR.

Apart from sale in Russian Federation, Polyoxidonium has been introduced also on the Japan medical market. It has been registered by the State Institute of Medicine Control of SR in the year 2001 under the registration number 59/0220/02-S.

These methodical recommendations introduce general information of the preparation; they contain also the mechanism of action; results of clinical studies of Polyoxidonium by patients suffering from chronic obstruction diseases of lungs, TBC, pyoderma, purulent-septic processes after chirurgical interventions, suffering from atopic dermatitis, inflammatory diseases of urinogenital tract, herpes-virus infections, HIV are stated in the pharmacokinetic characteristics. Polyoxidonium demonstrated a very good clinical effect in all these diseases. We have considered the introduction of optimum preparation use scheme in the case of every given nosological unit in these methodical recommendations necessary.

Immunomodulators

Still more immunorectifiers of different origin have been introduced into the clinical practice during the last years:
- Biological immunostimulators – tactivine, tymaline, tymotropine, tymogene, myelopid, leucinferon and other interferons
- Bacterial immunorectifiers – lycopid
- Synthetic immunorectifiers – diucifon and others.

The above stated immunorectifiers have a high efficiency.

Most of well-known immunorectifiers have a wide spectrum of effects but in connection with distribution of various forms of secondary immunodeficits there is an especially evident problem of targeted immunorectification. In connection with this question, there is an interest to search for immunorectifying preparations that are targeted at specific segments of immune system, therefore search for new proper immunorectifying preparations and study of their mechanisms of action is an up-to-date task of clinical immunology.

Preparations created on the basis of endogenous peptides produced by cells of immune system (tactivine, tymaline, tymogene, myelopid and others), influence predominantly processes of proliferation and differentiation of immuno-competent cells, and stimulate their functional activity on different levels.

Different kinds of interferons potentiate activity of killer cells, and stimulate as well different cells of immune systems by means of cytokines activation, including T-a, B- lymphocytes.

Lycopid preparation influences predominantly the monocytic-macrophagic segment of immunity, and stimulates actively the phagocytosis.

Works of R. V. Petrov, R. M Chaitov with co-authors show a new attitude towards search of immunorectifiers with selective affect on a particular segment of immunity, in the base of which a principle of immunogenes creation is established by means of structural unification of antigen and polymer – immunostimulator. Water-soluble poly-electrolytes are proposed as immunostimulators. It is proved experimentally that immune response to antigen complexes, conjugated with water-soluble poly-electrolytes is much bigger than a reaction to proper antigens. This quality enables wider manipulation when creating new immunostimulating preparations. Principally new synthetic immunostimulator – Polyoxidonium originated this way in the Institute of Immunology of RF HR.

1. Physical qualities

Name:	Polyoxidonium 0,003 g and 0,006 g for injections.
Chemical name:	co-polymer N-oxi 1,4-ethylenpiperazine and (N-carboxiethyl) – 1,4 ethylenpiperazine bromide with molecular weight 100 KD.
Appearance:	lyophilized porous substance with yellowish shade.
Solubility:	good soluble in water or isotonic solution of sodium chloride.
Stability:	storage temperature from +2 ^{0}C to +8 ^{0}C on a dry place, protected from light during 2 years. It is not recommended to store in the form of solution.

Drug form: ampoules or vials with lyophilized powder for injections, containing 3 or 6 mg of Polyoxidonium.

2. Pharmacological qualities

This Preparation has an immunomodulating effect; it increases the resistance of organism to local as well as generalized infections. It increases immune resistance of organism to infections induced by different microorganisms e.g. of series ***Salmonella, Shigell, Escherichia, Streptococcus*** and others. The basis of mechanism of immunorectifying effect of Polyoxidonium is a direct activation of phagocytosing cells and natural killers, as well as stimulation of antibody creation.

Apart from immunomodulating effect, Polyoxidonium has a proven detoxicating activity, relating to the macromolecular essence of preparation. Polyoxidonium increases the stability of cell membrane and chemical agents, and decreases their toxicity. Polyoxidonium stimulates the ability of reticuloendothelial system to catch and remove body-foreign micro elements from circulating blood. It is able to increase the adhesion of polymorphous-core leucocytes in blood and their capability to produce active forms of oxygen in contact with fragments of microorganisms.

Polyoxidonium is able to renew immune reactions in case of serious immunodeficiency status and primarily in case of secondary immunodeficiency status, caused by infections, injuries, burns, carcinomas, complications after chirurgical interventions, after administration of cytostatics, and steroid hormones. It is known that Polyoxidonium does not impair natural inhibition mechanisms; it doesn't exhaust spare possibilities of haematopoietic system when stimulating an immune reaction. On the contrary it increases the efficiency of natural postoperative mutual influence of T- and B-lymphocytes in reaction of antibody production.

Use of Polyoxidonium in complex treatment allows increasing of efficiency and decreasing of length of treatment; it reduces dosage of taken antibiotics, bronchospasmolytics, and glucocorticoids significantly, and prolongs duration of remission.

This preparation is well tolerated, has no mutagenic, polyclonal activity, antigenic qualities, and no allergenic activity.

Polyoxidonium is a water-soluble polymer, whose molecule consists of 1000 elementary segments. There is a large number of weakly charged groups (N-oxide groups) in a long polymer chain of Polyoxidonium that ensure high absorbent ability of this polymer. Each molecule of Polyoxidonium is able to create a complex with number of small molecules and mainly with toxin molecules.

Detoxicating potential of Polyoxidonium is very high; it is more than hundred times higher than in the case of the most popular detoxicating substance in medicine – hemodese. Therefore we may observe reduction of intoxication symptoms in seriously ill patients already within several hours after parenteral administration of Polyoxidonium.

Polyoxidonium increases the efficiency of antitumoural immunity. In the basis of antitumoural action of Polyoxidonium is its ability to activate neutrophiles and macrophages, which are very important elements of antitumoural protection. Treatment of oncological patients in several clinics proved that use of Polyoxidonium in combination with chirurgical treatment, irradiation or chemotherapy allows achieving better results in terms of prevention of complications and recession of tumours. Polyoxidonium consequently activates immunity, whereby it decreases the likelihood of tumour formation, and it inhibits growth of tumours that originated earlier.

3. Pharmacokinetics

Polyoxidonium is characteristic by its high bioavailability (89%), it achieves maximum concentration in blood via i/m administration after 40 minutes, and it spreads quickly into all organs and tissues. Period of distribution in organism (quick phase) is approximately 25 minutes, period of excretion (slow phase) – 36,2 hours via i/m and 25,4 hours via i/v administration. The preparation is liable to biodestruction and is excreted predominantly by kidneys.

Polyoxidonium doesn't cause side effects or toxic effects. There were no local or total reactions, side effects or complications recorded after the use of Polyoxidonium in any case. Therefore we may state convincingly that Polyoxidonium is absolutely harmless for human.

Use of Polyoxidonium is safe. This preparation is used in medicine for more than 6 years. More than 2 million people have received Polyoxidonium by injection. There were no side effects or complications recorded in any case.

Polyoxidonium strengthens immune, but not allergic reactions. Allergy is most often based on production of antibodies of IgE class, whereas defence against infections is determined by antibodies of IgG, IgA, IgM classes but not IgE class. Administration of Polyoxidonium leads to the activation of IgG and IgM synthesis and it never stimulates production of IgE. Therefore Polyoxidonium increases immune infection protection, but it doesn't increase allergic reaction.

Polyoxidonium may be combined with antibiotics, antivirus and antimycotic preparations, glucocorticoids and spasmolytic substances, vitamins, beta-carotenes, and cytostatics very well. Polyoxidonium is fully compatible with almost any medical treatment.

Polyoxidonium may be administered into the organism of patient by several ways – i/m, subcutaneously, i/v, and endolymphatically. Other ways of administration than via injection are used in case of concentration on the area of pathological process. This enables to activate so called local immunity, i. e. parts of immune system that are nearest to the ill organ or tissue. For example for the treatment of prostatitis it is efficient to administer Polyoxidonium rectally in the form of an insert. It is possible to administer Polyoxidonium under the tongue or to instill drops into the nose when treating inflammatory processes of nasopharynx or bronchi. These routes of administration are especially suitable for the treatment of children, because they enable avoiding injections.

Polyoxidonium may be administered repeatedly. Usual medical dose consists of 5 – 15 injections, applied i/m per 6 mg of Polyoxidonium. Repeated medical

doses may be carried out within 2-3 months interval. Patients react equally to the first, second and every next dose of Polyoxidonium. This means that resistance to Polyoxidonium doesn't originate.

Doctor chooses dose of Polyoxidonium and scheme of treatment individually for each patient. He takes into consideration the substance of illness, extent of symptoms of illness, acute or chronic development, ineffectual attempts of treatment in anamnesis and much more. It is also possible to formulate several universal principles (schemes), which could be used in medical practice.

4. Usage Instructions

The preparation activates immunity by adults and children. Most efficient use of Polyoxidonium is within traditional treatment, adequate to the illness. Polyoxidonium is well tolerated with antibiotics, antivirus, antimycotic and antihistaminic preparations, broncholytics, corticosteroids, and beta-agonists.

Polyoxidonium 0,006g is recommended for adults in complex treatment of:

- chronic recurring inflammatory diseases of any etiology that don't respond to traditional methods of treatment in the phase of complications, as well as in the phase of recurrence;
- acute and chronic virus and bacterial infections;
- acute, chronic, urinogenital and gynecologic infectious inflammatory diseases;
- allergic diseases (polynosis, bronchial asthma, atopic dermatitis), chronic recurring bacterial and virus infections with complications;
- as a prevention and treatment of local and generalized forms of purulent-septic diseases, and of postoperative complications in chirurgic patients;
- in the process and after chemotherapy and irradiation of tumours;
- to reduce nephro- and hepato-toxic effect of medicamentous preparations;
- to activate regeneration processes (fractures, burns, trophic ulcers);
- to rectify secondary immunodeficits, resulting from ageing or due to the effect of adverse factors.

5. Administration routes

This preparation is indicated for adults via i/m or i/v (via infusion) in doses of 6 – 12 mg once in 24 hours every day, two-times or once a week depending on the diagnosis and extent of illness.

Dissolve the content of ampoule or vial in 1,5 – 2 ml of isotonic solution of sodium chloride or water for injections for i/m administration. Dissolve the preparation in 2 – 3 ml of isotonic solution of sodium chloride, hemodese, reopolyglucan or glucose for i/v administration (via infusion), transfer sterilely to a vial with the abovementioned solutions in the volume of 200 – 400 ml.

SOLUTION CAN NOT BE STORED!!!

6. Recommended schemes of treatment for adults

Acute inflammatory diseases:
Administer per 6 mg every day for three days, then every second day in total medical dose 5 – 10 injections.

Chronic inflammatory processes:
Administer per 6 mg every second day, 5 injections, then two-times a week in total medical dose 10 injections.

Patients with acute and chronic urinogenital diseases:
Administer per 6 mg every second day in total medical dose 10 injections together with chemical preparations.

Chronic recurring herpes:
Administer every second day in total medical dose 10 injections.

Treatment of different forms of allergic diseases with complications:
Administer per 6 mg, total medical dose 5 injections: first two injections every day, then every second day. Administer i/v per 6-12 mg together with tavegil and other anti-allergic preparations in case of acute allergic and toxicoallergic condition.

Oncological patients:

- before and during chemotherapy to decrease immunodepressive, hepato- and nephrotoxic action of chemotherapeutic substances per 6 – 12 mg every second day in the total medical dose minimally 10 injections;
- long-term use of Polyoxidonium per 6 mg twice a week is prescribed to prevent immunodepressive impact of tumour, and to rectify immunodeficiency after chemotherapy and irradiation; after chirurgical removal of tumour.

Usage instructions for children from 6 months of age:

Polyoxidonium 0,003g is recommended for children in complex treatment of:

- chronic inflammatory diseases, induced by bacterial, virus, fungal originators of infection;
- acute infections inflammatory diseases;
- acute allergic and toxicoallergic cases;
- bronchial asthma, complicated by chronic infections of respiratory tract;
- atopic dermatitis, complicated by purulent infection;
- disbacteriosis of intestinal tract.

Administration routes

Ways of indication are chosen by the doctor depending on diagnosis, extent of illness, age and weight of the patient.

Parenterally (i/m or i/v via infusion) in the dose of 0,1 – 0,15 mg/kg per 48 – 72 hours in the total medical dose 5 – 7 injections. Dissolve the preparation in 1 –

1,5 ml of water for injections or in isotonic solution of sodium chloride for intramuscular administration. Dissolve the preparation in 1,5 - 2 ml of sterile isotonic solution of sodium chloride, polyglucan, hemodese or glucose for intravenous administration via infusion; transfer sterilely to a vial with the abovementioned solutions in the volume of 150 - 200 ml.

Sublingually – every day in the dose of 0,1 -0,15 mg/kg for 10 days.
Intranasally – per 0,05 – 0,1 mg/kg into each nostril 2 – 3 times a day for two days. Instill per 3 – 5 drops during 10 – 15 minutes. Two-day treatment is repeated in the interval of 48 hours. Up to 5 treatment doses are administered.

Dissolve 3 mg of Polyoxidonium in 0,6 ml of distilled water in case of intranasal or sublingual indication and use according to this scheme:

Age	Preparation amount	Dose
up to 1 year	2 - 3 drops	0,5 - 0,7 mg
1 - 3 years	3 - 4 drops	0,7 - 1,0 mg
3 - 5 years	4 - 5 drops	1,0 - 1,5 mg
5 - 7 years	5 - 6 drops	1,2 - 1,5 mg
7 - 10 years	8 - 12 drops	2,0 - 3,0 mg

6.1. Recommended schemes of treatment of children

- Chronic inflammatory diseases: per 0,1 mg/kg every second day in total medical dose 5 – 7 injections.
- Chronic inflammatory diseases per 0,1 – 0,15 mg/kg twice a week in total medical dose 7 – 10 injections.
- Acute allergic and toxicoallergic cases: administer i/v (via infusion) per 0,1 – 0,15 mg/kg together with tavegil and other anti-allergic preparations.
- Treatment of allergic forms of diseases with complications together with basic treatment: intramuscularly per 0,1 mg/kg in the dose 5 injections with 1-2 days interval.

6.2. What is known about mechanisms of action of Polyoxidonium?

Polyoxidonium interacts with external membrane of cells of immune system. Here, on the level of cell surface a signal is shaped that triggers a physiological reaction of cells as a response to the action of Polyoxidonium. Polyoxidonium initiates a chain of internal cell events that activate neutrophiles, macrophages and NK-killers. As a response to this action macrophages and neutrophiles catch body-foreign antigens more actively, they remove immune complexes from the blood flow intensively, they produce cytokines and interferons, which activate T- and B cell immune response, and they destroy microbes more efficiently. Above described cell events lead finally towards substantial change of functional activity of immune system, they increase efficiency of its response to body-foreign antigens, thereby strengthen the production of specific antibodies, as well

as cell immune reactions. This allows a quick and effective removal of infectious agent and its toxins.

6.3. Which useful qualities does Polyoxidonium have?

Main advantage of Polyoxidonium is poly-functionality of its positive effect on human organism. This poly-functionality of Polyoxidonium manifests itself apart from immunomodulating effect in detoxicating and antioxidant effects. Detoxicating effects manifest themselves in the ability of Polyoxidonium to excrete different toxins from organism. For example its use in complex treatment of burned patients and patients with pancreonecrosis significantly decreases many indicators of intoxication: of endotoxin, dialdehyde, diene acids. Antioxidant effect of Polyoxidonium is connected with its ability to catch active forms of oxygen and decrease the level of peroxide oxygenation of lipids in the membranes of cells. Redundant formation of active forms of oxygen is harmful for organism and may be the reason of development of many pathological states: cancer, early ageing, arteriosclerosis etc.

7. Technology (methodology) of Polyoxidonium's clinical use

It is known that there are three groups of immune system disease:

- Immunodeficient,
- Allergic,
- Autoimmune processes.

There are immunologic defects that manifest themselves by imbalance of cell sub-polarization, ratio of Th1/Th2 cells, level of immunoglobulin, and intracellular cytokines in case of all these pathologies. Principles of use of immunomodulating treatment have its peculiarities in every single of these groups.

<u>Allergic diseases.</u>

Use of Polyoxidonium in case of allergic diseases is suitable in the cases complicated by development and chronicity of infection centers of virus, bacterial or fungal origin. Effect of Polyoxidonium is in these cases directed at removal of infectious centre by the patient, what can substantially improve the clinical picture of primary disease.

<u>Autoimmune diseases.</u>

In case of autoimmune diseases most widely spread is the use of immunosuppressors, directed at suppression of acute inflammatory process. Their use has usually a good clinical effect. But complication of the above stated treatment may be development and chronicity of infectious centers. Therefore at present, also in the case or allergy, the basis for the use of Polyoxidonium in autoimmune processes is the infectious process, which complicates the course of primary disease.

<u>Immunodeficient diseases</u>

Increased infectious sickness rate is the principal manifestation of a primary, as well as secondary immune deficiency. A question emerges, whether the use of immunomodulating preparations (in this case mainly Polyoxidonium) in primary

immune deficiency, whose basis is a genetic defect, is efficient. Naturally, it is not possible to rectify a genetic defect by means of this preparation. But an anti-infectious defence is poly-componential and we may expect that by small increase by means of functional activity immunomodulators of a normally functioning component of immunity system, "the imperfect work" of defect element will be at least partially compensated. Besides that a long-term persistence of infect, constant connecting of new inflammatory centers induces gradual exhaustion of "genetically non-defective" components of immune system. It is possible to observe some improvements of clinical state and indicators of immune state by patients with decreased level of all classes of immunoglobulins (total variable immunological deficiency) by their treatment with immunomodulating preparations, which activate phagocytosis, as by the use of Polyoxidonium. Therefore well thought out use of immunomodulating treatment by patients with immune deficiency may cause good clinical result.

Main target of use of immunomodulating preparations are secondary immune defects that manifest themselves by frequent recurrence of infectious-inflammatory diseases of varied localization, which surrender to the treatment very hard. Examination of immune system parameters need not always find out these changes. Clinical course of chronic infectious diseases that surrender to the standard treatment hardly may serve as an indicator of preparation prescription, increasing anti-infectious protection, even though no changes of immune status were discovered.

It is most efficient to use immunomodulators to activate the anti-infectious immunity, which affect the cells of monocytic-macrophagic system, i. e. those, which induce centripetal activation of immunity corresponding to the natural course of development of immune answer. Apart from that, elimination of most of pathogen microbes from microorganism is realized finally by means of cells of phagocytic system. The preparation of first choice by treatment of chronic infections is Polyoxidonium.

In all cases when doctor prescribes anti-microbial substances for phenomena of secondary immunological deficiency, it is necessary to prescribe also the immunomodulating treatment, independently of whether changes of immune system of a given patient have been discovered or not. When treating these processes, immunomodulators are used mainly in **complex treatment** together with ethiotropic chemical therapeutic substances.

Basic criterion of prescribing an immunomodulator with prevailing effect on phagocytic system is detection of a chronic infectious process.

It is necessary to say that immunomodulators of Polyoxidonium type have to be prescribed *before* as well as *after* administration of antibiotics or antivirus preparations, but most efficient is its prescription *together with ethiotropic preparations*. The originator is in this case under "double impact": antibiotics or another chemotherapeutic substance decrease the functional activity of microbes and an immunomodulator increases the functional activity of phagocytic cells, thanks to what a more effective elimination of originator from organism is achieved.

The question of immunomodulators use in case of acute bacterial and virus infections is a different one. Usually prescription of immunotropic preparations in case of acute infection may induce development of an infectious process.

Exception to the rule is the immunomodulator Polyoxidonium, which activates monocytic-magrophagic element of immune system and simultaneously has a detoxicating and antioxidant effect, as well as an effect of membrane stabilization. Clinical practice points to the efficiency and safety of its use in case of acute infections.

Polyoxidonium may be used in case of immunorehabilitation measures as a mono-therapy in a complex with different strengthening substances. This is justified in case of patient's incomplete recovery (presence of bronchitis, laryngitis, tracheitis etc.) after overcoming acute infectious disease and in case of oncological patients for improvement of life quality.

Clinical studies of injection form of Polyoxidonium were realized in more than 700 patients in ten medical institutions of Russia. Polyoxidonium was used for treatment of patients with primary and secondary immune deficiency, allergic diseases, autoimmune processes (chronic obstruction diseases of lungs, TBC, pyodermatosis, purulent septic processes after chirurgical interventions, atopic dermatitis, inflammatory diseases of urinogenital tract, herpes virus infections, HIV). Clinical studies of Polyoxidonium were carried out in line with GCP rules (good clinical practice), using the double random blind control.

7.1. Use of Polyoxidonium by atopic dermatitis patients

Use of Polyoxidonium is pathogenetically justified and clinically effective in the forms of atopic dermatitis (AD) complicated by secondary infection. Besides the immunomodulating effect Polyoxidonium has a significant detoxicating effect and it can be used for the purpose of improving AD deterioration in a complex with infusion treatment. Immunomodulating treatment has to be carried out within the period of deterioration of the process, complicated by secondary skin infection in complex with parenteral administration of antibiotics, antihistamines, systemic glucocorticosteroids (GCS). The preparation is administered to adults in dose of 12mg/day i/v via infusion for 5 days, then per 6 mg/day every second day i/m up to 10 injections. The dose is calculated from 0,07 - 0,15 mg/kg for the treatment of children, depending on the extent of complications of the process i/v or i/m in the interval of two days in the total dose of 5 – 7 injections. Patients who suffer from atopic dermatitis tolerate this preparation well. There were no allergic or toxic reactions to Polyoxidonium, or changes of biochemical indicators of blood recorded in any case.

Basic clinical effects of Polyoxidonium involved in a complex treatment of atopic dermatitis are:

1. reduction of regression time of pyodermatosis centers
2. improvement of overall condition, depending on decrease of intoxication and skin itching
3. reduction of dose and shortening of administration period of systemic GCS.

7.2. Use of Polyoxidonium by patients with bronchial asthma

We could observe a decrease of antiinfectious immunity in case of serious bronchial asthma, mainly the one dependent on hormones, where the infectious-

allergic component plays an important role in the genesis. This disease progresses frequently in connection with recurrence of bacterial, virus and fungal infection centers (chronic purulent-obstruction bronchitis, chronic purulent haimoritis, mucosal-skin candidiasis etc.), what deteriorates the course of the primary disease. These patients receive additionally immunomodulating preparations in the complex treatment. Use of Polyoxidonium is most efficient (in the phase of deterioration or recurrence), it accelerates the stabilization of condition and helps to prolong recurrence. Polyoxidonium is used in complex treatment by adults according to the following scheme: per 6 mg i/m every second day N5, then per 6 mg for three days up to 10 injections. Children use Polyoxidonium according to this scheme: 0,1 mg/kg dose of 5 injections in the interval of 1-2 days. This treatment proved:

1. faster improvement of disease deterioration;
2. increase of resistance to infectious agents;
3. extension of remission period of chronic infection centers' deterioration;
4. extension of remission interval of bronchial asthma;
5. reduction of dose of systemic GCS;
6. accomplishment of ASIT treatment (allergenic specific immunotherapy) causally by significant allergens;
7. normalization effect on changed parameters of immune system condition;
8. reduction of hospitalization days, reduction of treatment price

There were no complications in the course of disease and no negative changes of laboratory indicators after administration of Polyoxidonium.

7.3. Use of Polyoxidonium in allergenic specific immunotherapy (ASIT) of atopic diseases, complicated by secondary immune deficiency

Forms of allergic disease lasting more than 5 – 7 years that are not complicated by chronic infection centers are rare, what complicates the accomplishment, but also lowers efficiency of ASIT.

Therefore to prepare the patient who has chronic infection centers, Polyoxidonium was prescribed per 6 mg i/m every second day for 10 days to accomplish ASIT together with complex treatment of detected virus or bacterial fungal centers of infection by adults. Children used Polyoxidonium in dose of 0,1 – 0,15 mg/kg of weight every second day 5 injections, then 2 injections weekly up to 10 injections. Effective immunorehabilitation was accompanied by immune reaction renewal, what allowed transition to accomplishment of ethiotropic treatment (ASIT) per 4 – 6 weeks. There were no complications discovered by the treatment of these patients.

7.4. Use of Polyoxidonium by rheumatoid arthritis patients

Glucocorticosteroid preparations, cytostatics, non-steroid anti-inflammatory preparations are used for treatment of rheumatoid arthritis, which have significant side effects, including development of secondary immune deficiency. This patient received Polyoxidonium in complex standard basic treatment

according to the scheme 6 mg i/m N5 – every second day and N5 – once in three days. After the treatment following was proved:

1. improvement of clinical symptomatology: decrease of painful syndrome, decrease of number of inflamed joints and Richi joint index, normalization of body temperature, there wasn't tendency to the weight loss, or improvement of mood and there were no depressive states observed;
2. decrease of ARVI sickness rate;
3. no side effects on the accomplished primary treatment;
4. improvement of laboratory indicators;
5. stabilization of primary disease after the treatment (observations were carried out within 6 months).

7.5. Use of Polyoxidonium by bronchial asthma patients

Polyoxidonium was prescribed to patients with chronic bronchitis in the phase of deterioration as well as in the phase of disease remission. Torpid, chronic, always recurring course of disease, no adequate answer to antibacterial treatment regardless of unchanged immune system condition, were a reason to prescribe Polyoxidonium.

All patients received Polyoxidonium together with complex treatment: antibacterial (considering sensitivity of flora), muco- and bronchiolytic, vitamin treatment, and physiotherapy.

Preparation was prescribed in dose of 6 mg/day i/m every second day up to 10 injections. First dose of Polyoxidonium may be increased to 12 mg/day depending on the extent of disease. If it is necessary, next scheme may be changed.

Patients who have chronic bronchitis tolerate this preparation well – there were no allergic or toxic reactions observed. Inclusion of Polyoxidonium into complex treatment helps to:

1. reduce the period of disease deterioration;
2. improve the overall condition, depending on decrease of intoxication, cough, hyper-production of sputum;
3. reduction of dose and shortening of administration period of systemic antibacterial, antimycotic preparations;
4. increase of resistance to infectious agents;
5. reduction of hospitalization days and reduction of treatment price;
6. extension of diseases' remission.

7.6. Use of Polyoxidonium by patients with overall variable immune deficiency (OVID).

Inclusion of Polyoxidonium in the complex treatment is indicated by patients with innate form of immune deficiency – OVID. This preparation is not primary by this nosology, but it is prescribed for rectification of secondarily changed (exhausted) elements of immune system. The preparation was used according to this scheme: 12 mg/day on 1., 2., 3., 5., 7., 9., 11. day of treatment. Besides that all patients received supporting dose of Polyoxidonium – per 6 mg i/m once a week for 3 months.

Inclusion of Polyoxidonium in the complex treatment of gamma globulin anemia patients helps to:

1. reduce the period of disease deterioration;
2. improve overall condition, depending on decrease of intoxication, cough, hyper-production of sputum;
3. reduction of dose and shortening of administration period of systemic antibacterial, antimycotic preparations;
4. increase of resistance to infectious agents;
5. reduction of hospitalization days and reduction of treatment price;
6. extension of diseases' remission;
7. normalization of leucocytes level, normalization of indicators of neutrophiles functional activity.

7.7. Use of Polyoxidonium by patients with different forms of lungs TBC

Inclusion of Polyoxidonium in complex treatment is indicated by patients with infiltrative, disseminating and fibroso-cavernose tuberculosis, together with tubercular preparations (izoniazide, riphampycine, pirazinamide, streptomycine, etambutol). Since characteristic feature of tubercular infection is deficiency of bactericide systems of macrophages for elimination of bacteria, activation of cells of monocytic-macrophagic system leads to increase of neutrophiles migration into inflamed center, strengthening of lysosomal enzymes activity, increase of phagocytes' ability to absorb and destroy microbes.

Polyoxidonium is prescribed per 6 mg i/m twice a week, dose of 10 injections. Basic effects of Polyoxidonium use are:

1. reduction of bacilli secretion period
2. intoxication symptoms disappear
3. acceleration of absorption process of infiltrating changes and closure of lungs destruction;
4. increase of monocytes' ability to absorb, reduction of genesis of active forms of oxygen, normalization of neutrophiles functional activity.

7.8. Use of Polyoxidonium by patients with chronic recurring furunculosis

Use of Polyoxidonium is pathogenetically substantiated and clinically efficient by chronic steady furunculosis, as well as by unchanged condition of immune system. Chronic recurring furunculosis is a polyetiologic disease, which is accompanied by many centers of chronic infection and changes of immune system condition. Phagocytic element is the most spread defect of immune system; therefore Polyoxidonium is prescribed to patients in connection with complex treatment. Immunotropic treatment has to be carried out within deterioration of the process, in a complex treatment of chronic infection centers. Preparation is prescribed in the dose of 12 mg/day i/m on the 1., 2., 5., 8., 11., 14. day of administration. Patients suffering from chronic recurring furunculosis tolerate this preparation well. There was no allergic or toxic reaction to administration of Polyoxidonium in any case. Basic clinical effect of Polyoxidonium's inclusion in the treatment of chronic recurring furunculosis is:

1. reduction of regression period of pyodermatosis centers;
2. overall improvement of condition, depending on decrease of intoxication;
3. reduction of dose and shortening of administration period of systemic antibacterial preparations;
4. increase of remission period;
5. normalization of immunological indicators: increase of CD 8+, CD 16+ lymphocytes, increase of phagocytic index, and indicators of functional activity of neutrophiles.

7.9. Use of Polyoxidonium in complex treatment of patients with significant endotoxicosis cases: by chirurgic patients with purulent-septic and infectious processes, by burned patients

Chirurgic diseases with purulent-septic complications and infectious processes, pancreonecrosis, burns, all have different etiologic aspects; however they are united by development of serious endotoxicosis, manifold deficiency, and significant symptoms of immunosuppression. This forecasts an unfavorable result of disease. Polyoxidonium's prescription is aimed at immunomodulation, membrane stability, detoxication and antioxidation. Polyoxidonium is administered every day once per 12 mg i/v for three days after operation, then every second day per 6 mg i/v in total dose of 10 – 15 injections.

Patients felt improvement of overall condition after use of Polyoxidonium in chirurgic practice, improved appetite, increase of tonus, normalization of temperature. We have recorded positive dynamics in the course of mediastinitis, bronchial-lungs complication, peritonitis, cleaning of wounds from purulent-necrotic stuff, decrease of swelling and soreness, closure of fistulas, acceleration of reparation processes. We have equally observed normalization of immune system condition (increase of CD 3+, CD 4+ and others).

Regardless of use of modern technologies in treatment of pancarditis, lethality may reach up to 80% by this pathology. Activation of process of peroxide oxidation of lipids (POL) plays primary role by genesis and development of functional and structural disorders of pancreas and of organism in general by acute pancarditis. Developing disorder of immune system by acute pancarditis may be explained also by functional deficiency of liver, by loss and deficient income of proteins. Use of Polyoxidonium aimed at immunomodulation, membrane stabilization, detoxication and antioxidation is therefore justified.

All patients tolerate treatment without complications. After treatment we have recorded:

1. decrease of lethality;
2. reduction of average hospitalization;
3. reduction of pancreas tissue sequestration;
4. acceleration of wound cleaning and acceleration of regeneration processes;
5. normalization of laboratory indicators.

We may point to very significant intoxication in the course of 7 – 10 days by serious burns and to development of infection in following weeks. After-burns toxaemia is connected with effect of toxic substances of different origin, which

circulate in the blood. Bacterial endotoxins that come to systemic blood flow by translocation of intestinal microflora are very important in significant after-burns toxaemia. Besides that after-burns wound is practically not sterile and wound infection also plays a significant role in intoxication development by patients with thermic trauma. Serious disorders of immune system of burned patients in the course of disease justify use of Polyoxidonium.

Use of Polyoxidonium in complex of medicamentous treatment of acute period of burns lead to:

1. quick normalization of body temperature, improvement of overall condition, as well as improvement of process of wound healing;
2. plausible decrease of transminases level, level of middle-molecular peptides, number of circulating immune complexes;
3. normalization of secretion of toxic elements from organism; decrease of bacterial endotoxaemia level.

It was discovered that Polyoxidonium did not cause side effects by serious burns in acute state of this disease.

7.10. Use of Polyoxidonium by patients with inflammatory urinogenital tract

Chlamydia trachomatis, Mycoplasma genitalium, Ureaplasma urealyticum, Trichomonas vaginalis occupy main place among urinogenital infections. Originators of infectious-inflammatory processes of urinogenital tract are at present characteristic by manifold antibiotics-resistance, and by atypical biological features. One of prime reasons of diseases' development, which are induced by opportunistic microbes, is decrease of immunological resistance of organism that enables low-virulent originators to display their pathogenetic features. This means, that treatment of chronic infectious-inflammatory processes has to be complex and it has to be composed of ethiotropic chemical-therapeutic substances, directed at elimination of originator and immunological substances, whose basic effect is increase of organism's resistance to infectious agents. Polyoxidonium is administered per 6 mg/day i/m for 1 – 2 days N 7 – 10. First dose of Polyoxidonium may be increased to 12 mg/day depending on the level of pathological process. Daily administration of first two doses of preparation is also possible, as well as an increase of number of injections to 15 per one treatment.

Direct endolymphatic administration of Polyoxidonium into peripheral lymphatic blood vessel of lower extremity via lymphatic catheter is possible in case of serious course of chlamydia prostatitis. Scheme of administration: every second day per 6 mg N 5 – 6.

Efficiency of Polyoxidonium's use in complex treatment was in:

1. total clinical recovery and death of originators in pathological material;
2. reduction of treatment period;
3. significant reduction of taken antibiotics;
4. decrease of disease recurrence frequency.

Chronic prostatitis is an inflammatory process, connected with changes of local and systemic immunity and with formation of secondary state of immune deficiency. Treatment represents significant difficulties in connection with long-

term recurring course, manifold character of etiologic factors and pathogenetic mechanisms of disease development, participation of several systems of organism – urinogenital, endocrinal, vascular, and immune. Polyoxidonium was used according to the scheme per 6 mg i/m every second day in total treatment of 10 injections.

All patients tolerated treatment satisfactorily. During treatment we could observe:

1. improvement of clinical state of patients (improvement of ache syndrome, diuresis prostatorrhoea);
2. no soreness by palpation, higher tonus – by objective examination;
3. improvement of local and systemic laboratory indicators;
4. stable clinical effect.

7.11. Use of Polyoxidonium by patients with herpes virus infections

Necessity of Polyoxidonium's involvement in the overall treatment scheme of patients with genital form of HSV – 1 and HSV – 2 is conditioned by several moments, from which one of the determining factors is appearance of herpesvirus strains resistant to basic antivirus preparations. Antivirus program of treatment, which contains combination of chemical and immune preparations, is pointed at suppression of virus replication and activation of antivirus immunity. Polyoxidonium was prescribed to these patients in the phase of disease deterioration. All patients received Polyoxidonium together with complex treatment: antivirus preparations from the group of synthetic tricyclinic nucleosides according to the standard scheme.

Polyoxidonium was prescribed per 6 mg/day i/m every day; total treatment represented 5 injections, or 6 mg/ day daily N5, then every second day N5. Analysis of patients' treatment proved an effect of addiction on dose; therefore it is advisable to use the second scheme of treatment.

Patients with herpesvirus infections tolerate this preparation well; no allergic or toxic reactions appeared. Involvement of Polyoxidonium in the complex treatment helps to:

1. reduce period of total re-epithelisation;
2. increase of remission length;
3. activate antivirus immunity (CD8+, CD16+, IFN-α, IFN-γ).

7.12. Use of Polyoxidonium by patients with lymph-pharynx circuit pathology

Observations of long-term ill or frequently ill children discovered a chronic inflammatory process of lymph-pharynx circuit (chronic adenoiditis, chronic tonsillitis, hypertrophy of palatal tonsils). Immunologic movements, which accompany development of adenoiditis, are a serious problem. Adenotonsilar hypertrophy is considered to be a result of chronic antigenic irritation. Objective examination of this category of patients discovered changes of nasocytogram, and increase of microbial dissemination.

Polyoxidonium was used according to the scheme: 0,15 mg/kg daily, treatment lasts 10 days. After treatment we have discovered:

1. normalization of nasal respiration, catarrhal phenomena disappeared;
2. improvement of subjective feeling – decrease of headaches, decrease of intoxication syndromes;
3. decrease of pharynx tonsil hypertrophy;
4. normalization of nasocytogram indicators;
5. decrease of bacterial colonization of upper respiratory tract membrane;
6. normalization of local humoral immunity indicators, activation of nonspecific factors of membrane defence (lysocim);
7. decrease of acute respiratory virus infection frequency, decrease of level of difficulties during its course.

There were no total or local side effects recorded after the use of preparation in any case.

7.13. Use of Polyoxidonium by oncological patients

Course of oncological diseases is accompanied by various changes of immunological system condition that worsen after accomplishment of immunosuppressive treatment (cytostatic treatment, radiotherapy).

Patients with mixed cell variant of Hodgkin lymphoma (LH) and histiocytosis (LKG) have positive failures of immunological reactivity: by children with LKG – prevailingly humoral and by patients with LH – cell immunity. Most of researchers point to the presence of interaction defect between T – cells and macrophages. This was one of the reasons to prescribe Polyoxidonium into complex treatment of mentioned diseases.

Polyoxidonium was prescribed to children from 5 years of age per 3 mg/day, i/m and to children older than 5 years – per 6 mg/day. Regime of Polyoxidonium use: before chemotherapy – every day, for 5 days, further in the process of chemotherapy: in case of LH (first two treatments) – three-times a week, up to 20 doses, in case of LKG – two weeks three-times weekly and six weeks twice a week, together 23 doses.

We could observe 20-30% decrease of tumor's size after 5 doses of Polyoxidonium taken before treatment, as well as a partial balancing of ratio of immunoregulating cells. Use of Polyoxidonium after chemotherapy demonstrated a more significant regress of tumorous forms in comparison with control group, and a renewal of immune reaction. Thus prescribing Polyoxidonium in combination with chemotherapy by patients with LKG and LH achieves total effect in shorter period.

We have observed a total regress of neoplasm of soft tissue by children with histiocytosis after 5-day chemotherapy treatment (prednisone + vepezid + vinblastin). We have documented a 70-80% regress of tumorous lymph nodes by patients with mixed cell variant of Hodgkin lymphoma after 1 chemotherapy treatment (prednisone + vincristine + cyclophosphane + natulan + doxorubicin) and a total effect after two treatments of chemotherapy. Regress of lymph nodes was slower by patients with nodular sclerosis of Hodgkin disease.

Polyoxidonium was used per 6 mg i/m, in the total dose of 9 injections by the treatment of breast cancer together with adjuvant chemotherapy according to the scheme + radiotherapy of breast area (FAC + radiotherapy). This scheme of

treatment wasn't interrupted by any patient due to a bad tolerance or development of infectious complications.

Involvement of Polyoxidonium in the complex treatment of oncological diseases enables:

1. improvement of patient's condition in the course of treatment;
2. to increase the efficiency of standard anti-tumorous treatment;
3. to decrease the toxic effect of radio- and chemotherapy;
4. to decrease the number of infectious complications in the course of treatment;
5. to stimulate leucopoiesis and normalize immunological indicators;
6. to decrease the probability of disease recurrence.

Traditional ways of tumor treatment are irradiation, cytostatic chemotherapy, and surgical intervention. Several comparing researches confirm the existence of immunodepressive effect of cytostatic treatment by treatment of tumours. There is a great amount of compiled facts in literature about the possibility of forecasting results by accomplishment of cytostatic treatment. We can say that there is a higher risk of bad prognosis for patients by decrease of immunological indicators during or after conclusion of following cytostatic treatment, in comparison with those patients who have not decreased immunological indicators.

Most frequent complications of radiotherapy are cytopenic syndrome and state of immunodeficiency. Immunodepressive statuses develop most frequently by application of radiotherapy before surgical intervention directed at reduction of tumour's size. It is not possible to ignore the fact of possible development of immunodepression after surgical intervention due to the effect of preparations on narcosis, wound surface, stress.

Effect of chemical preparations is connected with damage of cytomembranes or break of tumor cell metabolism. This effect spreads in a certain amount to the cells of bone marrow and immune system. Cyclophosphane, vincristine, metotrexate, and cytosinarabinosid have the greatest immunodepressive effect. Development of cytopenic syndrome may be conditioned directly by cytotoxic effect on bone marrow cells, as well as by development of suppressor effect of T-lymphocytes on the system of blood creation.

We can set aside a group of tumours that are resistant to cytostatic treatment when comparing results of malign tumorous diseases treatment. That is for example melanoma, cancer of kidney. These tumours are characteristic by high degree of malignity; i. e. quick growth and early development of metastases characteristic is for them.

Polyoxidonium has the same pharmacologic features as immunomodulating and detoxicating substances, what allowed achieving good clinical and laboratory indicators by use of this preparation for treatment of patients with different kinds of tumours. All tumours may be divided formally into three groups:

1. immunologically very sensitive tumours (melanoma, cancer of kidney and urinary bladder);
2. medially immunologically sensitive tumours (cancer of large intestine, lymphoma);
3. low immunologically sensitive tumours (breast cancer, cancer of lungs).

Different methods of parameters' determination of cell and humoral element of immunity, indicators of peripheral blood were used to evaluate efficiency of Polyoxidonium's use.

Effect of Polyoxidonium was used variously taking into consideration different immunological sensitivity of tumours:

1. to remove suppressor effect of T-lymphocytes on blood creation system;
2. to strengthen effect of chemical preparations, mainly by treatment of tumours resistant to cytostatic treatment;
3. for prevention of distant metastasisation;
4. for prevention of post-operation complications.

Two variants of use of Polyoxidonium were applied in treatment of patients with immunologically very sensitive tumours: a) in connection with a-INF when the objective was to cumulate endogenic IL-2; b) in connection with IL-2. Accomplishment of combined treatment of Polyoxidonium a-INF and IL-2 induced a positive result in 80% of cases by the treatment of patients with melanoma and kidney cancer, by treatment of diseases resistant to irradiation and chemotherapy. These recombinant preparations a-INF were used: Intron A, Roferon, Vellferon, recombinant IL-2. Polyoxidonium was administered prevailingly per i/v, in single dose of 6 mg, in the interval of 2 – 3 days, by serious degree – every day. Regardless of presence of distant metastases by most of the patients (95%), more frequently in lungs, brain, bones, a slowdown of metastasisation, and necrosis of primary tumour's center was achieved, in a number of cases of distant metastasis removal.

It is necessary to emphasize that irradiation and chemotherapy was not carried out in these cases. This means that there were no complications observed by these patients, which are characteristic for traditional cytostatic treatment.

Use of Polyoxidonium in connection with chemical preparation by treatment of medial sensitivity of tumours enables strengthening of cytostatic effect by direct activating effect of Polyoxidonium on cells and functions of immune system. Higher quality, longer-term remissions were achieved by using Polyoxidonium and traditional polychemotherapy treatments by observing a group of patients with large intestine tumour, and lymphoma. Treatment of these diseases involved prevailingly such chemical preparations as cyclophosphane, metotrexate, vincristine, vinblastin, fluorouracil, which often induce cytopenic toxic complications. All patients who received Polyoxidonium felt well, 28 % of patients with large intestine cancer diagnosis and 48% of patients with lymphoma diagnosis achieved remission of disease.

Connecting use of Polyoxidonium and radiotherapy by treatment of tumours sensitive to irradiation enabled faster achievement of positive effect. We could observe cytopenic and immunodepressive complications, by patients in a lower measure in comparison with control group. All patients felt better subjectively.

Use of Polyoxidonium in connection with a cytostatic treatment as palliative method by inoperable and terminal states was directed at prolongation and improvement of life quality, probably thanks to detoxicating feature of this preparation.

Conclusions:
Clinical results of use of Polyoxidonium with traditional methods of tumour treatment proved justification of Polyoxidonium's use for rectification of immunological disorders, emerging on the background of cytostatic irradiating, chemical treatment, interpheronotherapy, stabilization of cell membranes against harmful effect of free radicals that emerge by the abovementioned treatment methods, and also with the objective of detoxication.

7.14. We can hear frequently that any stimulators, including immunostimulators, may stimulate growth of tumour. Is it so? What is known about Polyoxidonium's effect on formation of tumours or growth of an already existing tumour?

To take stimulators of immunity as stimulators of tumour's growth is possible only on the basis of consonance of names. This opinion is not right. Most of immunity stimulators do not activate, but in a certain measure inhibit growth of tumours.

Special investigations demonstrated that Polyoxidonium has no cancerogenic effects. Besides that this preparation significantly increases the efficiency of antitumour immunity. The basis of antitumour effect of Polyoxidonium is its ability to activate neutrophiles and macrophages that are very important elements of antitumour defence.

Treatment of oncological patients on various clinics showed that use of Polyoxidonium in combination with chirurgical treatment, irradiation or chemotherapy enables to achieve better results in terms of prevention of complications and recurrence of tumours.
This means that by activation of immunity Polyoxidonium decreases the probability of tumour's origination; it inhibits development of previously originated tumours.

7.15. Use of Polyoxidonium by diabetes patients

Diabetes is often complicated by development of centers of chronic infection (chronic pyelonephritis, purulent necrotic attack of lower extremities and others). Long-term disorder of saccharine transformation leads to the development of endotoxicosis. In connection with this we observe symptoms of immunosuppression: centers of virus, bacterial and fungal infection, vascular diseases that are hard to treat by traditional basic methods. This has become the basis for introduction of immunomodulator Polyoxidonium into the complex of medical measures. This preparation was administered per 6 mg i/m every second day, whole treatment was 30 mg (5 injections). After this treatment one could find:

1. improvement of clinical count of disease – significant decrease of painful syndrome in quiet state, decrease of paraesthesia, burnings, horripilation;
2. improvement of local process: regressive development of trophic disorders, delimitation and tearing off necroses on soles, change of wet gangrene to a dry one;
3. possibility to achieve stabilization of state by conservative measures;

4. decrease of endotoxicosis phenomena;
5. decrease of volume of chirurgic interventions;
6. improvement of laboratory indicators.

7.16. Use of Polyoxidonium by patients with endogen hypercorticism

We can observe symptoms that indicate development of immune system disorders and activation of chronic infections centers (chronic pyelonephritis, pyoderma, fungal affection of nails) by increase of cortisol level in blood of patients. Treatment of this group of patients involves Polyoxidonium in complex treatment according to the scheme: per 6 mg i/m every second day, treatment of 10 injections. After treatment one could find:

1. reduction of period of chronic pyelonephritis, decrease of spotty skin;
2. decrease of number of postoperative complications;
3. improvement of subjective condition;
4. normalization of laboratory indicators.

8. Indications and contraindications

As the completed researches demonstrated, Polyoxidonium is a highly efficient preparation with curative effect.

Its most effective use is in connection with traditional therapy, corresponding to disease. Polyoxidonium may be combined with antibiotics, antivirus, antifungal and antihistaminic preparations, broncholytics, corticosteroids, cytostatics, and adrenomimetics. Indicators of Polyoxidonium's involvment in the complex treatment are as follows:

1. presence of chronic recurring bacterial, virus and fungal infection;
2. diseases with significant symptoms of endotoxicosis (chirurgic diseases with purulent-septic complications, pancreatitis, burns, diabetes, oncological diseases and others);
3. balancing of negative consequences of immunosuppressive treatment, as well as nephro- and hepatotoxic effect of medicamentous preparations.

8.1. Is it possible to use Polyoxidonium by allergic, atopic patients and patients with bronchial asthma?

This question worries in fact every doctor, who hasn't used Polyoxidonium yet. Use of substances that activate immune reactions may really strengthen allergic reactions or atopy. Therefore many immunomodulators and immunostimulators can not be used by allergic and atopic patients. This inhibition does not apply to Polyoxidonium. This preparation is permitted and used with success as an immunomodulator by allergies and bronchial asthma.

Polyoxidonium strengthens immune, but not allergic reactions. Allergy is most often based on the production of antibodies of IgE class, whereas infection defence is determined by production of antibodies of IgG, IgA, IgM, but not IgE class. Administration of Polyoxidonium leads to the activation of IgG and IgM synthesis, whereby it does not stimulate production of IgE. Therefore Polyoxidonium strengthens immune infection defence, but it does not strengthen

the allergic reaction. Even at the peak of the most serious allergy, so called acute toxic-allergic reaction (ATAR) it is possible and necessary to administer Polyoxidonium intravenously (via infusion). This increases efficiency of detoxicating treatment in a large measure. Besides that Polyoxidonium prevents purulent septic complications, which nearly always follow ATAR by activation of immune infection defence.

Great need of Polyoxidonium's use emerges by the treatment of allergy or bronchial asthma, which are complicated by chronic infection. Atopic dermatitis is for example frequently complicated by purulent dermatitis. Serious forms of bronchial asthma are nearly always complicated by chronic bronchitis. The complication of both diseases rests on the fact that an infectious disease is accumulated on the atopic process. Effective treatment of infectious inflammation is not possible without activation of anti-infectious immunity. It is dangerous to activate immunity of atopic and allergic patients due to possible strengthening of atopy's allergy. Polyoxidonium solves the problem, because it activates immunity without strengthening of allergy and atopy.

It is necessary to include Polyoxidonium in the conventional treatment by the treatment of abovementioned variants of allergy, atopy and bronchial asthma complicated by infectious inflammation. This will increase efficiency significantly. Polyoxidonium activates immune infection defence; it inhibits infectious inflammation, and decreases its manifestations. Consequently purulent septic complication of atopic dermatitis is efficiently treated or chronic infection in bronchi is stopped, which are the factors worsening the course of bronchial asthma.

9. Which ways of Polyoxidonium's administration are allowed?

Polyoxidonium may be administered into patient's organism by several ways – intramuscularly, subcutaneously, intravenously, endolymphatically. Non-injection ways of administration are used in case of concentrated treatment in the area of pathological process. This allows activation of so called local immunity, i. e. parts of immune system that are nearest to the affected organ or tissue. It is efficient to administer Polyoxidonium rectally in the form of an insert by the treatment of prostatitis. It is possible to administer Polyoxidonium under the tongue or to instill drops into the nose when treating inflammatory processes of nasopharynx or bronchi. These routes of administration are especially suitable for the treatment of children, because they enable avoiding injections.

10. Is it possible to repeat medical doses of Polyoxidonium, and how often?

Polyoxidonium may be administered repeatedly. Usual medical dose represents 5 – 15 intramuscular injections per 6 mg of Polyoxidonium. Repeated treatment may be accomplished in the interval 2 – 3 months during the treatment. Patients react equally well to the first, second and all consequent treatments by Polyoxidonium; this means that resistance to Polyoxidonium doesn't emerge.

11. According to which symptom is it possible to determine that a patient is indicated for Polyoxidonium?

It is recommended to determine the condition of immunity in an ideal situation already before deciding whether an immunomodulator is to be administered. But this is an ideal situation. Reality forces us frequently to decide without a preceding research. It is necessary to take into consideration all symptoms of immune deficiency in this case.

In following clinical situations the doctor may be convinced that patient suffers from immune system deficiency and an activation of immunity by means of Polyoxidonium is indicated:

1. almost any chronic inflammation;
2. recurring inflammatory diseases, such as acute respiratory diseases, bronchitis, herpes, furunculosis and others;
3. if anamnesis contains several attempts of treating inflammatory processes by means of antibiotics, antivirus and antifungal preparations;
4. by serious development of acute inflammatory process or by appearance of symptoms of surface inflammatory process' transition into a deep, local – diffused one;
5. by torpid recovery (healing) of acute inflammatory process, appearance of tendency of change to a chronic disease.

New products on the basis of Polyoxidonium

1. Rectal inserts

Rectal inserts 0,006g, Nr. 10 are sold freely for more than two years

Instructions of medical use of rectal inserts with 0,006g; 0,0012g of Polyoxidonium (Suppositoria rectalia cum Polyoxidonia 0,006 g, 0,012g.)

Composition

Rectal inserts with Polyoxidonium per 0,006g; 0,0012g have a torpedo form, white colour without aroma, on the basis of stiff fat, or yellowish colour with slight aroma, on the basis of cocoa butter. Active substance is Polyoxidonium.

Pharmacological features

Polyoxidonium contained in suppositories has an immunomodulating effect; it increases resistance of organism to local and general infections. Basic mechanism of immunomodulating effect of Polyoxidonium is direct impact on phagocytic cells and natural killers, as well as stimulation of antibodies' production.

Use of Polyoxidonium in complex treatment enables to increase efficiency of treatment, significantly decrease dose of antibacterial and antivirus substances, to reduce the treatment period.

Polyoxidonium renews immune reactions by difficult forms of immune deficiency and mainly by secondary immunodeficiency cases, induced by infections, for example tuberculosis, as a consequence of ageing, complications of chirurgical operations, injuries, burns, treatment by cytostatics, and steroid hormones.

Besides of immunomodulating effect Polyoxidonium has also a provable detoxicating activity, which is determined by polymer basis of preparation. Polyoxidonium increases membranes' resistance to cytotoxic effect, it decreases toxicity of medical preparations.

Pharmacokinetics

Polyoxidonium in rectal suppositories has a high availability; it achieves maximum concentration in blood within an hour after administration. Period of excretion in quick phase is approximately 30 minutes; period of excretion in slow phase is 36,2 hours. The preparation metabolizes in organism and is excreted predominantly by kidneys.

Indication of use

Rectal suppositories with Polyoxidonium are used by adults in complex treatment of secondary immune deficiencies that manifest themselves in acute and chronic recurring infectious-inflammatory processes. Polyoxidonium is well tolerated with antibiotics, antivirus, antifungal and antihistaminic preparations, broncholytics, corticosteroids, cytostatics, and adrenomimetics.

Use of inserts with Polyoxidonium is recommended in connection with an adequate traditional treatment of adults for the treatment of:

1. chronic recurring inflammatory diseases of any etiology, which are resistant to traditional methods of treatment in acute phase as well as remission phase;
2. acute and chronic virus and bacterial infections (including urinogenital and gynecologic infectious-inflammatory diseases): prostatitis, urethritis, cystitis, chronic pyelonephritis in latent phase and in acute phase, chronic salpingo-oophoritis, metro-endometritis, colpitis, diseases induced by papilloma virus, ectopy of cervix, dysplasia and leucoplakia);
3. tuberculosis;
4. acute, chronic allergic diseases (polynosis, bronchial asthma, atopic dermatitis), complicated by chronic recurring bacterial and virus infection;
5. during and after chemotherapy and tumour irradiation;
6. to decrease nephro- and hepatotoxic effect of medical preparations;
7. to prevent and treat local and generalized forms of purulent-septic diseases, postoperative complications by chirurgical patients;
8. for activation of regeneration processes (fractures, burns, trophic ulcers) ;
9. for rectification of secondary immunodeficits, which emerge due to the effect of adverse factors and ageing.

Way of administration and doses

Preparation is administered to adults rectally once a day for night after cleanup of intestinal tract per 0,1 - 0,2 mg/kg (one insert 6 mg or 12 mg). The dose is chosen depending on the body weight, acute phenomena and difficulties of the process. Scheme of administration: first three days it is administered every single day and then in the interval per 48 hours. Medical dose is 10 inserts. If it is necessary treatment can be repeated after 3 – 4 months.

Long-term use of Polyoxidonium is indicated (from 2 – 3 months up to 1 year) per 6 – 12 mg once to twice a week to prevent immunodepressive effect of tumour, to rectify immunodeficit after chemotherapy and irradiation.

Side effects

Side effects were not detected.

Contraindication

Pregnancy

Medicamentous form

Rectal suppositories containing 0,006 or 0,012g of Polyoxidonium

Storage

On a dry place, protected from light, by temperature 4 – 6 ^{0}C

2. Pills with Polyoxidonium

This medicamentous form is already in the final phase of putting into practice. Indication for its use is the same as in the case of injections or suppositories. Oral administration is supposed to be directed at gastro-intestinal tract area in the pathological process.