Review Article

Basic principles of pharmacotherapy of diseases of the visual organs

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ABSTRACT

By origin, eye diseases can be primary (the result of exposure to mechanical stimuli) and secondary (arising against the background of the disease of the whole organism). A number of eye diseases are accompanied by a violation of the outflow of blood and lymph, which causes hypertension and secondary lesions of various parts of the eyeball and a violation of its visual functions. The article describes various methods of treatment of infectious eye diseases since the middle of the last century. The main goal of treatment is to create an optimal concentration of drugs in the focus of the disease for a certain time. Currently, in the treatment of purulent keratitis, there has been a significant increase in interest in various types of coatings that allow isolating the cornea from mechanical trauma, environmental exposure, as well as retaining medications on the affected cornea. This article describes in detail modern methods of treating keratoconjunctivitis, including antibiotic therapy, the use of various synthetic films, and exposure to a diode laser. In particular, it mentions the disadvantages of the listed methods.

Keywords: Antibiotic therapy, Diseases of the organ of vision, Eyes, Keratoconjunctivitis, Blood-aqueous barrier

Introduction

Diseases of the visual organ are common pathologies in humans. By origin, eye diseases can be primary and are most often the result of exposure to mechanical stimuli (wounds, bruises, foreign objects) and secondary, arising against the background of a disease of the whole organism (infectious hepatitis, metabolic disorders) [1].

The development, nature, and outcome of secondary eye diseases are poorly understood. It is possible that some changes in the visual analyzer, mainly its internal parts, and, in particular, the bottom of the eye, may be mistaken for natural anomalies or variations in the normal state. Hence, there is a definite need to study secondary eye diseases and their impact on the state of vision [2].

A number of eye diseases are accompanied by a violation of the outflow of blood and lymph, which causes hypertension and secondary lesions of various parts of the eyeball, and a violation of its visual functions.

It was found that minor damage to the conjunctiva during purulent processes sharply exacerbates the pathological process [3, 4].

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Basic principles of pharmacotherapy of diseases of the visual organs

It is generally recognized that antibiotics are among the most powerful means of treating infectious diseases caused by various pathogenic bacteria. In this regard, the search for new, even more, effective antibiotics is one of the urgent problems of modern biology and medicine. The exceptionally high antimicrobial activity of antibiotics opened wide paths for them

in medicine, where they began to be used not only for treatment but also for the prevention of various diseases [5].

In the 50s of the last century, when conducting pathogenetic therapy for keratitis, some experts suggested using novocaine blockade through the subglacial canal [6].

In the 60s of the last century, some experts concluded that oletetrin, dibiomycin, and syntomycin have the greatest biological activity in relation to rickettsias and microflora of the external eye of patients with rickettsiosis keratoconjunctivitis. Under the influence of these antibiotics, rickettsias and sensitive strains of microbes disappear in smears of conjunctival scrapings and the contents of the conjunctival sac after their use, while simultaneously attenuating inflammatory phenomena and faster recovery.

In the 70s of the last century, some specialists with rickettsiosis keratoconjunctivitis used daily insertion of 30% sulfacyl-sodium ointment or 10% synthomycin emulsion into the conjunctival sac. In the subsequent stage, the best therapeutic effect was observed with the combined use of 30% sulfacyl-sodium ointment or 10% synthomycin emulsion with retrobulbar novocaine blockade.

In the 80s, some specialists used an emulsion of yellow mercury oxide, oriprym in powder and a solution of novocaine, after thoroughly mixing the components, fish oil was added to the mixture and brought to a creamy consistency. It was applied with forceps to the conjunctiva at a dose of 0.2 ml once a day for 2 weeks, and then a day later until complete recovery [7, 8]. Later, ocular therapeutic films with tetracycline (oxytetracycline) and novocaine were developed [9].

In addition to the described methods of exposure, a 3% solution of boric acid, a solution of ethacridine lactate 1:1000, penicillin, ichthyol, iodoform, yellow-mercury ointment were also used for rickettsiosis keratoconjunctivitis. Sulfonamide preparations (dust and ointments) and penicillin on fish oil had the greatest therapeutic effect.

Other treatment options were: 5% berenyl ointment, which accelerates the recovery process and prevents corneal damage; 3% xeroform emulsion on fish oil, mercury monochloride, Lugol solution, yellow mercury ointment; ofloxacin, which is an antimicrobial drug from the group of broad-spectrum fluoroquinolones.

Some scientists with infectious and invasive keratoconjunctivitis received a high therapeutic effect from ocular therapeutic films with sodium sulfapyridine, neomycin sulfate, kanamycin sulfate, and ditrazine citrate when injected into the conjunctival sac [7, 8].

Thus, for therapeutic and prophylactic purposes in rickettsiosis keratoconjunctivitis, we tested: dibiomycin and tetracycline ointments, 10% syntomycin emulsion, and oletetrin powder. The use of these drugs in the stage of abscess and ulcers, as a rule, does not prevent the formation of persistent scarring. Tetracycline ointment, although it softens the course of the disease, but the inflammatory phenomena do not completely go away: there is a moderate injection of sclera vessels, swelling of the eyelids, lacrimation, and photophobia - the process takes a protracted course.

Complications in the organs of vision with irrational antibiotic therapy

In medicine, all therapeutic drugs, including antibiotics, are used according to strictly established, scientifically based prescriptions. Each of the drugs is prescribed by a doctor for the treatment of certain diseases; at the same time, it is indicated in what dose, when, and how many times the medicine should be used. An arbitrary increase in the dose, lengthening the duration of use, shortening the intervals between them, etc. can lead to undesirable side effects of the drug - complications. The cause of complications often remains unknown. Some scientists explain them by the peculiarity of the chemical structure of antibiotics, others by the action of toxins formed as a result of the decay of microorganisms under the influence of antibiotics used in "shock" doses. Still, others explain the frequency of these phenomena by the uncontrolled use of antibiotics in home practice.

The role of staphylococcus in various diseases has significantly increased, which is explained by the development of its resistance to antibiotics. Cases of infectious lesions caused by Pseudomonas aeruginosa have become more frequent. As is known, the treatment of staphylococcal and pseudomonas infections presents particular difficulties [10].

Currently, in the treatment of purulent keratitis, there has been a significant increase in interest in various kinds of coatings that allow isolating the cornea from mechanical trauma, environmental exposure, as well as retaining medications on the affected cornea. Various materials of synthetic and biological origin are offered as coatings today [11].

In addition, it is proposed to use eye medicinal films with various drugs. These dosage forms have a prolonged bio-soluble base in their composition, the presence of which makes it possible to exclude frequent administration of the drug, while at the same time ensuring its accurate dosing. The use of ocular medicinal films allows for the preservation of the natural protective film of the cornea, which is destroyed with frequent instillations, promotes the regulation of the cellular and fibrous composition of the organizing connective tissue [11, 12].

In medical ophthalmology, there is a large list of medications that have different routes of administration (parenteral, local: topical, and locally injected), which can become one of the causes of undesirable effects. Local treatment of the eye is based on topical application (drops, ointments) or local injection of drugs (subconjunctivally, retrobulbar, or into the anterior chamber of the eye). Damage to the cornea and conjunctiva quite often occurs when applying drops or ointments, because they are structures that protect the eye, which directly comes into contact with the environment and, in particular, with medications (pathology of "contact"). Local irritation causes a tingling or burning sensation and manifests itself in the form of blepharospasm. These effects are explained by the pH difference or osmolarity of the tear, as well as the action of the active or formative substance of the drug. Each drug according to its construction (active substance, filler, or formative

substance – placebo, preservative) can cause the effect of hypersensitivity [13]. The particular sensitivity of the eye, apparently, is associated with the thinness of the conjunctiva, its enrichment with mastocytes, pronounced drainage of the lymphatic system, an excess of blood vessels, and the presence of immunocompetent cells. All medications can cause sensitivity mainly if there are local conditions conducive to this (insufficient tears, excessive blood filling, maceration, etc.). Some medications may inhibit scarring of the damaged cornea. Prolonged and insufficiently selected antibiotic therapy (indications and the course of appointment are not adapted) can contribute to the selection of resistant flora [14, 15].

Infectious keratoconjunctivitis often causes atrophy of the eye in patients, this is because the vessels are partially desolate and dissolve, but most of them remain in a state of significant blood filling. Probably, the process can pass to the vascular membrane. With infectious rhinotracheitis, hyperemia and swelling of the mucous membrane of the eyes are observed. At first, the separable liquid, transparent, then becomes mucopurulent, turning into purulent. This is due to a decrease in the amount of lysozyme in the lacrimal fluid and the development of secondary infection. Chronic changes on the part of the cornea (opacities and scarring) lead to visual impairment.

The possibility of developing an intraocular infectious process in general septic and infectious diseases, as well as in the presence of a focal infection in the body, is not excluded. At the same time, any organs can serve as a source of endogenous infection of the damaged eye: teeth, tonsils, nose and paranasal sinuses, gastrointestinal tract, urinary tract, genitals, etc. However, the development of endogenous infection in the eyeball is possible even without the presence of any general infectious disease or a local infectious focus, since there are always sources for such infection of the eye in a clinically healthy organism [16].

The role of the blood-aqueous barrier in the pharmacokinetics of antibacterial drugs

The concept of the blood-aqueous barrier includes the structural and functional organization of tissue and cellular formations of the organ of vision, providing and maintaining the state of homeostasis of eye structures and determining to a large extent the features of the types of pathological reactions.

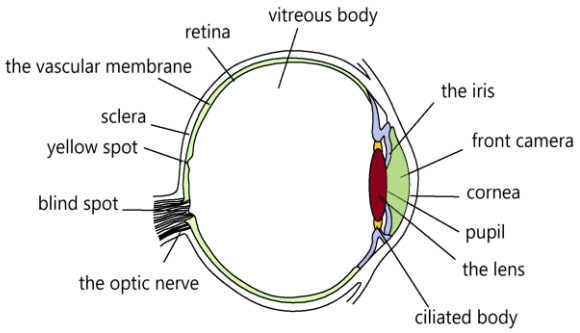

Figure 1. Schematic structure of the human eye [17]

There are two main barrier systems in the eyeball. The first of them is blood–intraocular fluid. It consists mainly of the structures of the ciliary body, which regulate and determine the nature of the relationship between blood and intraocular activity. In this case, the main movement of metabolites is carried out from the blood into the eye. The second barrier is blood-retinal. **Figure 1** shows the schematic structure of the human eye.

The difference between the blood-aqueous barrier is that the blood capillaries in the eye do not directly come into contact with cells and tissues. The entire complex exchange occurs through tissue (intercellular, interstitial) fluid. Blood capillaries are normally impervious to erythrocytes, leukocytes, and platelets. The interstitial fluid is delimited in the interstitial (intercellular) spaces between the basal membranes of capillaries and cell membranes. The blood flowing through the capillaries is separated from the surrounding tissues by the endothelium. Everything is at the ultrastructural level and is characterized by mechanisms of capillary, cellular, and membrane permeability. The structural links of the blood-aqueous barrier are anatomically autonomous, but functionally interconnected and are in continuous interaction and interdependence [18].

Some scientists propose to consider the blood-aqueous barrier as a set of 3 blood-tissue systems - iridociliary, chorioretinal, and papillary **(Table 1)**.

The papillary system is a connecting link that unites the blood-aqueous and blood–brain barriers into a single hydrostatic complex "brain cavity - eye cavity".

When the blood-aqueous barrier is violated, shaped blood elements (in particular monocytes) penetrate the vitreal chamber, which differentiates into macrophages and take an active part in the proliferative response.

Table 1. Blood-aqueous barrier

Blood-tissue systems	Blood-tissue structural elements
Iridociliary	Endothelium of capillaries of the ciliary body and iris, the basal membrane of capillaries, ciliary epithelium, and Bruch membranes of ciliary processes
Chorioretinal	Endothelium of capillaries, the basal membrane of choriocapillaris capillaries of the choroid, Bruch's membrane, retinal pigment epithelium, endothelium, and basal membrane of retinal capillaries
Papillary	Endothelium of capillaries, the basal membrane of capillaries of the dense network of the prelaminar part of the optic nerve, and neuroglia of the disc zone. The membrane function is performed by long processes of astrocytes separating nerve fibers from capillaries

Most often, diseases of the central organ of the urinary system – the kidneys - lead to the development of secondary retinopathy.
In conditions of pathology, the blood-aqueous barrier becomes permeable to various endogenous, exogenous, and other substances.
The study of the permeability to antibiotics showed that they penetrate the normal eye in small quantities, and least of all with intravenous and intramuscular administration. The highest concentration in the chamber moisture is observed with subconjunctival injections of the drug, and in the cornea – with topical application in the conjunctival sac [19]. The maximum therapeutic concentration of the drug when installing or placing ointment in the conjunctival sac is observed in the first 30-60 minutes, and after 2 hours it decreases or disappears. After administration under the conjunctiva, the highest concentration of the drug was noted after 3 hours, it disappears after 12 hours. With the disease, the barrier function weakens and the antibiotic penetrates the eye in greater quantities, nevertheless, the drug does not stay in the cornea and chamber moisture for a long time (maximum 60 minutes), but is eliminated after 2-3 hours [20]. The rapid removal of the drug from the chamber moisture is associated with its constant current and exchange [21-23].

Modern methods of pharmacocorrection of the permeability of the blood-aqueous barrier

Undoubtedly, the main goal of treatment is to create an optimal concentration of drugs in the focus of the disease for a certain time. Insufficient penetration of drugs to pathologically altered tissues cannot give a positive therapeutic result.
According to experimental and clinical data, the technique of creating zones of increased permeability of the blood-aqueous barrier in the area of the flat part of the ciliary body using a diode laser makes it possible to create a therapeutically significant concentration of drugs in the vitreous depot [24].
To date, there is a method of drug delivery to the posterior segment of the eye, which is effective and low-traumatic. The essence of the method is to create "windows" in the retinal pigment epithelium with a diode laser with a wavelength of 810 nm. Subtenon administration of drugs is carried out against the background of local vasoconstriction with a 10% solution of phenylephrine to reduce the absorption of the drug into the blood [25]. This makes it possible to achieve therapeutic concentrations of drugs in the vitreous depot, which in clinical practice is manifested by an improvement in visual functions in patients with glaucoma optic neuropathy.
The introduction of drugs under the conjunctiva using zones of increased permeability allows for achieving their maximum concentration in the posterior part of the eye. In addition, the synthesis of its own biologically active substances that can affect the level of metabolic processes and vascular tone is launched. This low-traumatic technique avoids possible complications characteristic of other methods of administration [26].
Also, achieving the optimal concentration of the drug in the lesion is achieved by choosing the dose and interval of administration. The standard treatment regimen provides for a 10-14-day course of injections in a hospital setting, which is a significant disadvantage. Daily administration of drugs leads to additional traumatization of the structures of the eyeball. In addition, the hospitalization of patients, an increase in the number of injections increases the material costs of both the patient and the hospital.
To improve the quality of life of patients, the optimal solution would be to reduce the number of injections to 1-2 times, which would also significantly facilitate conservative therapy in outpatient settings. When using prolonged-acting drugs due to the slow but constant release of the drug from the enriched form with a single injection, you can get a constant concentration of the active drug in the tissues for a long time. Currently, polymer-based substances, in particular, viscoelastic, are used to increase the viscosity (prolongation) of medicinal substances [20, 27, 28]. Modern methods of pharmacocorrection of the permeability of the blood-aqueous barrier are few and difficult to apply in practice.

Conclusion

Despite a huge breakthrough in the development of various eye treatment techniques, including microsurgical practice, the issues of the development of secondary pathologies of the visual organ against the background of the disease and antibiotic therapy are not sufficiently studied. A comprehensive study of the pharmacokinetics of antibacterial drugs in the organ of vision is necessary, as well as the study of the possibility of pharmacocorrection of the permeability of the blood-aqueous barrier for further development of a comprehensive treatment regimen that takes into account the possibility of secondary pathologies of the organ of vision.

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