ISSN 2231-2218

ASIAN JOURNAL OF PHARMACEUTICAL AND BIOLOGICAL RESEARCH

AJPBR

Indexed by:

ROAD Crossref Universal Impact Factor IMPACT FACTOR SEARCH

Asian journal of Pharmaceutical and biological research 2231-2218
http://www.ajpbr.org/
Universal IMPACT factor 7
SJIF 2022: 4.465
Volume 11 Issue 3
SEPT.-DEC. 2022
https://doi.org/10.5281/zenodo.7332728

Asian journal of Pharmaceutical and biological research 2231-2218
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Universal IMPACT factor 7
SJIF 2022: 4.465
Volume 11 Issue 3
SEPT.-DEC. 2022
https://doi.org/10.5281/zenodo.7332728

Medical treatment open angled glaucoma. Review.

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Abstract. Despite the progress of ophthalmology, the treatment of glaucoma remains one of the most important problems in this area of medicine. Traditionally, the main place in the treatment of glaucoma is taken by drug therapy. Thanks to the progress of pharmacology, the arsenal of antiglaucoma drugs has significantly replenished. However, a large selection of drugs creates certain difficulties for the practitioner: it is becoming increasingly difficult to understand the huge flow of scientific and advertising information about new drugs. This review aims to summarize the results of the most important experimental and clinical studies on betaxolol, one of the most effective treatments for glaucoma.

Keywords: glaucoma, betaxolol, timolol, b-blockers

Introduction. Currently, according to various authors, from 66 to 105 million people in the world suffer from glaucoma, and in the structure of the causes of irreversible blindness and low vision it accounts for about 29%. Scientists estimate that by 2020 the number of people blinded due to glaucoma was approximately 11 million [1]. About 1 million patients are registered in Uzbekistan, more than 150 thousand are visually impaired, of which about 70 thousand people have become blind as a result of glaucoma [4]. Medical and social problems of glaucoma are associated with the difficulty of diagnosing the early stages of the disease, the lack of a well-developed clinical examination of the population, as well as radical and effective methods of treatment. The only proven efficiency in the treatment of glaucoma, regardless of its form, is the reduction and stabilization of intraocular pressure (IOP) to an individually safe level. There are three ways to normalize ophthalmotonus: antihypertensive drug therapy, laser and surgical intervention. However, given that none of them gives a guaranteed lasting result, but at the same time each has certain risks, indications and contraindications, it is customary to choose a method with maximum efficiency and safety, and treatment of a newly diagnosed patient with glaucoma should be started with the appointment of local antihypertensive therapy. The need for daily and often lifelong adherence to instillation makes the problem of choosing the drug extremely important, taking into account the presence of systemic diseases, their therapy, and the interaction of medications received by the patient.

Thus, when prescribing local hypotensive therapy for patients with glaucoma, especially considering the fact that the main cluster of patients belongs to the older age group and this is often combined with the presence of certain chronic diseases, accompanied by the need for constant intake of systemic drugs, it is important to take into account the possible consequences of drug interactions between groups of drugs,

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the effect of antihypertensive drops on the course of general diseases, or the effect of general medications on ophthalmotonus and the course of the glaucoma process [3].

Beta-blockers. Drugs in this group are drugs that reduce the production of intraocular fluid. Beta-blockers, according to the degree of selectivity of action, are divided into non-selective (timolol maleate, etc.) and selective (betaxolol).

Timolol maleate - blocks β1 - and β2 -adrenergic receptors, does not have internal sympathomimetic and membrane-stabilizing activity. Inhibits central sympathetic impulses, weakens the sensitivity of peripheral tissues to catecholamines. The mechanism for reducing ophthalmotonus is to inhibit the secretion of intraocular fluid by blocking β-adrenoreceptors of the ciliary body. But, according to some reports, with long-term use of thymolol at the initial stages of glaucoma, there is an improvement in the indicators of the outflow of aqueous humor, which may be associated with a deblock of the scleral sinus.

The drug is indicated for all forms of glaucoma, both in monotherapy and in combination with other drugs of local antihypertensive action. Timolol penetrates through the cornea into the moisture of the anterior chamber well, is absorbed into the systemic circulation (the development of systemic effects is possible) [5].

Contraindications:

•the drug is not recommended for corneal dystrophies and dry eye syndrome (local use of β-blockers causes a decrease in tear production, deterioration of the function of the meibomian glands, which causes a violation of the stability of the tear film and leads to the development of xerotic changes in the epithelium of the tissues of the ocular surface);

• bronchial asthma, chronic obstructive pulmonary diseases (as a result of blockade of β_2-adrenergic receptors of bronchi, timolol increases their tone and can cause bronchospasm);

• sinus bradycardia, heart failure, atrioventricular block II – III degree, cardiogenic shock (blocking β-adrenoreceptors of the heart, drugs of this group cause bradycardia and reduce the force of heart contractions, resulting in reduced cardiac output, they also have the ability to inhibit atrioventricular conduction myocardial automatism) [2].

Beta-blockers are prescribed with caution in patients with diabetes mellitus, as they prolong drug hypoglycemia. These drugs can mask some of the symptoms of an overactive thyroid gland (eg, tachycardia). In patients with hypothyroidism, the reflex reaction time changes. Timolol can cause symptoms similar to those of myasthenia gravis (eg, diplopia, ptosis, general weakness). Despite the fact that β-blockers lower blood pressure, they should be used with caution in patients with Rhine's syndrome and pheochromocytoma, since a sharp increase in blood pressure is possible.

Side effects of timolol maleate:

• from the nervous system and sense organs: dizziness, headache, asthenia, fatigue, sleep disturbance, insomnia, nightmares, depression, agitation,

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hallucinations, short-term amnesia, disorientation in space, paresthesia, increased symptoms of myasthenia gravis; noise in ears;

- eye irritation, visual impairment, diplopia, ptosis, dryness of the mucous membrane of the eyes; with local use: rarely transient blurred vision (from 30 s to 5 min), burning, itching, sensation of a foreign body in the eye, changes in refraction and visual acuity, lacrimation, photophobia, decreased sensitivity of the cornea, edema of the corneal epithelium, inflammation of the eyelid margins, conjunctivitis , blepharitis, superficial punctate keratopathy, keratitis;
- from the respiratory system: nasal congestion, chest pain, cough, shortness of breath, suffocation, bronchospasm (possibly fatal), respiratory failure;
- from the cardiovascular system (hematopoiesis, hemostasis): palpitations, symptomatic bradycardia, arrhythmia, AV blockade, cardiac arrest, heart failure (possibly fatal), hypotension, collapse, Reynaud's syndrome, cold extremities, exacerbation of intermittent claudication, transient violation of cerebral circulation, cerebral ischemia, syncope, decrease in hemoglobin, hematocrit;
- others: angioedema, withdrawal syndrome, body weight change, lupus syndrome, weakening of libido, impotence, Peyronie's disease, hyperkalemia, hyperuricemia, hypertriglyceridemia [2-4].

Taking into account the fact that timolol maleate is the most commonly used drug in Russia, the issue of its interaction with other drugs is of particular importance Joint use of local non-selective β-blockers and antiarrhythmic drugs (amiodarone, diltiazem), sympatholytics, selective calcium channel blockers (verapamil), quinidine drugs increases the likelihood of violations of automatism, conduction and contractility of the heart muscle. In combination with drugs that deplete catecholamines (reserpine) and calcium channel antagonists, there may be an increase in effects such as lowering blood pressure and bradycardia. Thus, with the simultaneous systemic and local use of β-blockers, a mutual enhancement of the effects is possible (an additional decrease in IOP and an increase in the β-adrenergic blocking effect on the cardiovascular system) [1, 3].

Care should be taken when using β_1-, β_2-adrenergic blockers and adrenergic psychotropic drugs together: the latter affect peripheral innervation, with the most pronounced α-adrenergic blocking effect, as a result of which there is a decrease in the force of heart contractions, a drop in blood pressure up to the development of orthostatic hypotension ... It is dangerous to combine drugs of this group with antidepressants - MAO inhibitors (nialamid), since a hypertensive crisis may develop. The action of such agents as typical and atypical β-adrenergic agonists (izadrin, salbutamol, oxifedrine, nonahlazine, etc.), antihistamines (diphenhydramine, diprazine, fencarol, diazolin, etc.), glucocorticoids (prednisolone, budesohydrocortisone, etc.) when combined with β-blockers is weakened [9].

Inhibitors of the isoenzyme CYP2D6, such as quinidine and cymetidine, can increase the plasma concentration of timolol. Concomitant use with insulin or oral

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hypoglycemic agents may cause hypoglycemia. Timolol maleate enhances the effect of muscle relaxants; therefore, it is necessary to discontinue the drug 48 hours before the planned surgical intervention under general anesthesia [4].

Betaxolol is a selective β_1-adrenergic blocker without intrinsic sympathomimetic activity. When applied topically, it reduces IOP by reducing the production of intraocular fluid. Indications for use and the mechanism of hypotensive action is similar to that of timolol maleate, but the degree of decrease in ophthalmotonus is significantly lower than when using non-selective β-blockers.

Betaxolol, in comparison with other β-adrenergic blockers, does not cause a decrease in blood flow in the optic nerve, since it has practically no effect on vascular β_2-adrenergic receptors. There is experimental and clinical evidence of its neuroprotective action by improving hemodynamics and influence on calcium channels [7]. Betaxolol can be used to treat glaucoma or ocular hypertension in patients with respiratory problems. But with the simultaneous use of betaxolol and non-selective β-blockers for oral administration, the risk of side effects (both local and systemic) increases due to the additive effect. Therefore, patients receiving such combination therapy should be under special medical supervision.

When betaxolol is used in combination with drugs that deplete catecholamines (for example, reserpine), there may be a decrease in blood pressure and bradycardia. For more than 15 years, a new class of drugs for the treatment of glaucoma has not entered the market. As a result, problems began to appear with effective, but long-used first-line drugs for the treatment of glaucoma, such as allergic reactions and tachyphylaxis when treated with β-blockers and even changes in orbital tissues when prescribing prostaglandin analogs [3]. But given the need for long-term treatment of patients with primary glaucoma, a serious problem, according to many researchers, is the use of the preservative benzalkonium chloride in most eye drops [2]. Its long-term exposure to the surface of the eye causes toxic damage to the epithelium of the cornea and conjunctiva, goblet and other cells, which is clinically manifested by inconsistency of the precorneal film, corneal epitheliopathy, etc. density of subepithelial collagen, fibroblasts, immunocompetent cells, a decrease in the amount of extracellular matrix and goblet cells, a change in the cells of the nuclear-cytoplasmic ratio [4]. According to our study, the improvement of the state of the epithelium of the cornea and conjunctiva occurs 2 months after its replacement with a preservative-free drug. The test with lissamine green after 2 months of xonef BK administration revealed a significant reduction in the number and area of staining sites in the open palpebral fissure ($p < 0.05$).

Probably, a similar sanogenetic mechanism (regeneration of a full-fledged epithelium of the ocular surface) also has a tendency, revealed by us, to restore the stability of the precorneal film in patients with glaucoma. The trend towards normalization of Norn's test parameters in these patients had no statistical

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significance, apparently due to the short time period after discontinuation of the drug containing benzalkonium chloride, which was insufficient to restore the functions of the conjunctival goblet cells - producers of the mucin layer of the precorneal film [4].

It is known that long-term instillations of β-blockers cause secondary dry eye syndrome, which has a multicomponent mechanism of development [6]. The total tear production according to the Schirmer test in the group of patients was within the normal range (19.1 ± 10.6 mm). In 8 patients (16 eyes), hyposecretion was initially detected (according to Schirmer's test - less than 15 mm) - they used drops of β-blockers for more than 3 years. The use of xonef BC for 2 months did not significantly affect the total tear production in patients with glaucoma ($p < 0.05$).

Treatment of patients in the overwhelming majority of cases involves the appointment of antiglaucoma antihypertensive drugs in a constant and long-term mode, which can serve as a key factor in the intensification of the manifestations of signs of xerosis of the ocular surface or to their onset. An important role is played by the presence or absence of a preservative in the definite medicine, as well as the type of drug substance [6-8].

Currently, almost all antiglaucoma drops contain a preservative that protects the bottle and its contents from bacterial contamination. Due to its broad spectrum of antimicrobial action, benzalkonium chloride (BC) is recognized as the most effective preservative. It is able to dissolve bacteria membranes even in low concentrations (from 0.004 to 0.025%). A number of foreign authors in studies on animals and epithelial cell cultures have proved the cytotoxic effect of HD [10-11].

The impact on the epithelium of the anterior segment of the eye occurs as follows: getting with the dosage form on the ocular surface, HD, possessing the properties of a detergent, emulsifies the lipid component of the precorneal tear film, thereby creating direct access to the corneal epithelium. At the next stage, HD is adsorbed on epithelial cells, interacts with phospholipids of cytoplasmic membranes, causing their lysis, and penetrates into cells, which leads to intracellular disorganization and apoptosis [4, 5]. In a similar way, the destruction of the epithelial lining of the conjunctiva and the included goblet cells secreting mucin, which is responsible for the water-mucin component of the precorneal lacrimal film, occurs. In addition, long-term use of drugs containing HD as a preservative triggers a cascade of inflammatory reactions from the tissues of the anterior segment of the eye [6-8]. The direct effect of HD as a detergent on the lipid layer of the tear film leads to its destruction, which naturally leads to an increase in the evaporation of the water component of the tear film, an increase in osmolarity and the provocation of an inflammatory process in the tissues of the ocular surface [12]. The result of instability of the tear film and insufficient wettability of the epithelium of the cornea and conjunctiva is a decrease in the effect of protection from the action of the preservative.

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The cytotoxic effect of HD can lead to a slowdown and reduction in the number of mitoses and cell migration, which is associated with the effect on the cytoplasmic membranes, changes in the movement of calcium ions, and the emergence of an energy deficit in mitochondria. The end result of disturbances in bioenergetic processes is apoptosis and cell necrosis [9-11]. The cytotoxic effect of HD also extends to the limbus region, where stem cells are located, which provide constant regeneration of the epithelium [12]. Disruption of the processes of mitosis, migration and differentiation of stem cells, as well as their possible apoptosis when exposed to HD leads to a slowdown in the regeneration of the corneal epithelium, which is another factor that aggravates the direct toxic effect of the preservative on the ocular surface tissue.

The cytotoxicity of BCH (as part of an antiglaucoma antihypertensive drug) was assessed on the cell culture of the limbal stroma of the cornea in an experimental study at the Federal State Budgetary Scientific Institution "NIIHB" in 2017. In this work, the protective effect of the tear substitute Stillavit was also evaluated. The results indicated the toxic damaging effect of the drug containing latanoprost and HD on the cells of the limbal stroma. The level of cell viability when the drug (latanoprost + BH) was added at 100% concentration was 13.95 ± 4.014% of the control values. The positive protective effect of the tear substitute Stillavit in combination with this antihypertensive drug has been proven both at their 100% and 6.25% concentration. The results obtained made it possible to substantiate the advisability of using tear substitutes in patients with glaucoma who use antihypertensive drugs for a long time to relieve signs of epitheliopathy and its prevention [13].

Conservative treatment of glaucoma involves the appointment of local antihypertensive drugs for a long time to maintain a normal level of ophthalmotonus. The effectiveness and safety of the drugs used is the most important aspect, since glaucoma is a chronic disease that requires constant treatment. Good tolerability of the prescribed medications is of great importance for patient compliance with the recommendations of the doctor and the regimen for the use of eye drugs. The use of prolonged preparations with a low concentration of the active substance contributes to the achievement of safety and good tolerability of BBs with sufficient antihypertensive efficacy.

Long-term prescription of BAB requires research tear production and the state of the corneal epithelium tsy 1 time in 6 months, as well as control of visual fields with what kind of frequency. Appointment of BAB for topical use should be accompanied by monitoring of systemic indicators of arblood pressure, pulse, blood glucose in type 1 diabetes mellitus, lipid proloin. Years of clinical experience confirms that BABs can continue to be used as monotherapy or in combination with other drugs groups. Convincing evidence is neededsti refusal to prescribe drugs of this group for the time being not presented.

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