UDC 615.457.07

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SUBSTANTIATION OF A COMBINED MEDICINE DEVELOPMENT, INTENDED FOR GLAUCOMA TREATMENT, AS A PART OF THE DRUG TARGET PROFILE QUALITY

In order to determine one of the elements of the target product quality profile (intended application in clinical setting, route of administration, dosage form, strength of the dose), search and analysis of the available information concerning pathogenesis, therapies and drug products for treatment of glaucoma were conducted. These researches allowed substantiating relevancy and promising directions in combining drugs that affect different chains of pathogenesis, and creation based thereon of an effective drug in the form of eye drops, that helps optimizing current treatment of glaucoma.

Key words: glaucoma, intraocular pressure, irreversible blindness, antihypertensive therapy, combined drugs, lipid peroxidation.

FORMULATION OF THE PROBLEM

Identification of the target product quality profile, a key element of pharmaceutical development, forms the basis for planning the drug development, namely its intended application in clinical setting, safety and efficacy based on route of administration and dosage form, bioavailability, potency and stability. Plan of the drug development involves the use of data sources from different fields of science, including preclinical and clinical studies, results of which help solving the above issues.

Glaucoma is polyetiological severe chronic eye disease that takes the lead among the causes of irreversible blindness, obcecation and primary disability worldwide [9, 15, 17-19]. Pharmacotherapy of glaucoma is aimed at normalization of intraocular pressure (IOP), intraocular blood circulation improvement and normalization of metabolic processes in the retina and optic nerve, and includes multimodality therapy with several drugs having differently directed action [17, 25]. At the same time the goal of glaucoma treatment must be achieved with the help of the most effective and safe drugs used at minimal dosing regimen [8]. Chronicity of the disease, requiring long-term and continuous treatment, and elderly age of most patients suffering from comorbidities and taking other medicines (drugs), demands taking into account the peculiarities mechanism of the drugs action and their pharmacodynamics, as well as presence of local and systemic side effects [8]. The most effective and convenient for the patient is therapy with the help of combined medicines containing composition of several drugs. When using several mono-drugs there is a risk of additional eye irritation and washing-out of previous preparation at every successive instillation, resulting in significant reduction in the therapy effectiveness. Moreover, given the need for local daily antihypertensive therapy and continuous dynamic medical diagnostic observation, glaucoma refers to «expensive» diseases, which treatment is inaccessible for a part of elderly patients, leading to increasing of disability. Provision of free drops for a patient suffering from glaucoma in Ukraine in 2012 was worth UAH 2007 [5]. Given the above, improvement and development of new effective ophthalmic drugs, which would ensure not only normalization of IOP, but also stabilization of visual function, combined with minimal side effects and affordable to the general population, is always relevant.

ANALYSIS OF RECENT RESEARCH AND PUBLICATIONS

Glaucoma is a disease that ranks top in the list of eye diseases and is an important medical and social problem, as evidenced by statistics on the number of patients with glaucoma and visually

impaired people among them, chronic nature of untreated disease and irreversible loss of vision, difficulty of early diagnosis and the level of financial expenses for medical treatment. In the world, in the rating of causes of vision complete loss glaucoma ranks the second, 6 % to 20 % of all the disease cases end in blindness [15, 17]. Primary open-angle glaucoma represents about 90 % cases of all types of glaucoma [15, 17]. In Ukraine, within the structure of the primary disability glaucoma in 2006–2009 moved from fourth rank to the ranking second and accounted for 17.2 % of all the people with disabilities first recognized. In 2010, the total number of patients with glaucoma in Ukraine amounted to 226 thousands, which is 599.2 per 100 thousand people, first diagnosed glaucoma amounted to 23.3 thousand, which is 61.8 per 100 thousand people [15].

According to the modern concepts, «glaucoma» brings together a large group of eye diseases with different etiology, which have a number of common features in the pathogenesis, clinic and methods of treatment. Currently, there is no common understanding as regards terminology, causes and mechanisms of this disease, risk factors, and classification. There are several main stages of glaucoma pathogenesis [17–19]: violations and worsening the outflow of aqueous humor from the eyeball cavity, which may be due to various reasons; IOP increased above tolerance level for a specific eye; worse blood circulation in the eye tissues; hypoxia and ischemia tissues in optic nerve exit area; compression of the nerve fibers in the exit area from the eyeball with violation of their functions and destruction; degeneration, destruction and atrophy of optic fibers, degradation of their parent cells in retina; the development of glaucomatous optic neuropathy (GON), followed by optic nerve atrophy and incurable loss of vision.

The main goal of glaucoma treatment is aimed at preventing visual function decline, preservation of sight and, ultimately, maintenance of acceptable quality of life. Pharmacotherapy, surgery and laser therapy may be used for glaucoma treatment [17, 18, 25]. The choice of treatment technique depends on the form of glaucoma, patient's anamnesis, comorbidities [7]. However, original and basic technique of glaucoma treatment is pharmacotherapy, which may be used throughout the patient's life and may be employed after surgical or laser operations [17, 18, 25].

SELECTION OF EARLIER UNRESOLVED PARTS OF THE GENERAL PROBLEM

In the literature there are works describing combination therapy of glaucoma with the help of hypotensive eye drops and eye drops belonging to other pharmacological groups, which by combined use may significantly improve treatment outcomes [9, 23]. Clinical researchers indicate that it is desirable to develop combined eye drops for glaucoma treatment, including namely the substances with differently directed action that form a part of these mono-drugs.

FORMULATION OF THE ARTICLE PURPOSES

Using the principle of management knowledge from different fields of science, which exists in a public domain, namely, analysis of up to date information on causes, pathogenesis, treatment methods and finished drugs, the aim of this study was to assess relevance and promising trends in creation of combined dosage forms for glaucoma treatment.

PRESENTATION OF BASIC RESEARCH MATERIALS

Prognosis of the disease depends on pharmacotherapy, namely on the drugs ability of IOP lasting decrease. To this end, a key role for nearly 150 years in the medical treatment of glaucoma has been played by antihypertensive therapy, aimed at lowering IOP, which is achieved with the help of drugs with different mechanisms of action: some of them reduce formation of intraocular fluid, others increase outflow of intraocular fluid. During the years of glaucoma pharmacotherapy an arsenal of drugs was developed, many of which (physostigmine, phosphacolum, arminum, adrenaline, etc.), from the perspective of modern scientific knowledge, clinical experience and availability of more up-to-date medicines, have been out of use for a while. Specification of drugs for antihypertensive therapy is being represented by a wide range of mono- and combination medicines, mainly in the form of eye drops for topical application. List of basic modern antihypertensive drugs, according to the pharmacological groups and mechanisms of action is presented in Tables 1-2 [6, 7, 11, 14, 17].

Traditionally, the treatment of glaucoma begins with monotherapy drugs of first choice, which includes drugs group β-blockers (Timolol) and prostaglandin analogues (Latanoprost, Travoprost) [7, 17, 25]. Traditionally, treatment of glaucoma begins with monotherapy with drugs of first choice, which include drugs group β-blockers (Timolol) and prostaglandin analogues (Latanoprost, Travoprost) [7, 17, 25]. As a result of research in the CIS countries [8] it was found, that the first choice drugs at the start of treatment, regardless of the disease stage are (in descending order) β-blockers, combined medicines and prostaglandin analogues.

Table 1

SPECIFICATION OF MONO-PREPARATIONS FOR ANTIHYPERTENSIVE THERAPY

Pharmacologi-cal group	**Reduction in IOP, % to the baseline**	**Dosing regimen**	**Drug substance, drug concentration**	**Trade name**	**Dosage form**
Drugs that improve outflow of intraocular fluid					
Prostaglandins	25-33	1 time a day	Latanoprost 0.005 %	Xalatan, Lanotan	Eye drops
			Travoprost 0.004 %	Travatan	
			Tafluprost 0.0015 %	Taflotan	
M-cholinomime-tics	17-20	3-4 times a day	Pilocarpine 1 %, 2%, 4 %, 6 %	Pilocarpine-Pilocarpine hydrochloride	
Drugs that reduce production of intraocular fluid					
Non-selective β-blockers	20-25	2 times a day	Timolol 0.25 %, 0.5 %	Glaumol, Cusimolol, Oftimol, Arutimol	Eye drops
Selective β-blockers	20	2 times a day	Betaxolol 0.25 %	Betoptic C	
			Betaxolol 0.5 %	Betoptic, Betalmic	
α- and β-blockers	20	2-3 times a day	Butylaminohydroxy-propoxyphenoxyme-thyl methyloxadiazole 1 %, 2 %	Prodoxadol	
Carbonic anhydrase inhibitors	20	2-3 times a day	Acetazolamide 250 mg	Diacarb, Diuremid	Tablets
			Brinzolamide 1 %	Azopt	Eye drops
			Dorzolamide 2 %	Trusopt	

Table 2

SPECIFICATION OF COMBINED EYE DROPS FOR ANTIHYPERTENSIVE THERAPY

Trade name of combined medicine	**Drug substances, drug concentration**		**Dosing regimen**	**Reduction in IOP, % from baseline**
Xalacom, Lanotan T	Timolol 0.5%	Latanoprost 0.005%	1 drop once a day	25–34
DuoTrav	Timolol 0.5%	Travoprost 0.004%	1 drop once a day	27–34
Ganfort	Timolol 0.5%	Bimatoprost 0.03 %	1 drop once a day	28-33
Cosopt	Timolol 0.5%	Dorzolamide 2%	1 drop twice a day	25–30
Azarga	Timolol 0.5%	Brinzolamide 1 %	1 drop twice a day	25–30
Combigan	Timolol 0.5%	Brimonidine 0.2 %	1 drop twice a day	up to 33
Fotil	Timolol 0.5%	Pilocarpine 2%	1 drop twice a day	25–30
Fotil forte	Timolol 0.5%	Pilocarpine 4%	1 drop twice a day	25–30
Proxophelin	Clonidine 0.25%	Proxodolol 1%	1 drop 2-3 times a day	≈25
Proxocarpine	Pilocarpine 1%	Proxodolol 1%	1 drop 2-3 times a day	≈25

It has been found out that quantity of β-blockers prescriptions significantly exceeded the number of prescriptions for other groups of anti-hypertensive drugs, and in 67.34 % of cases theses were the drugs of choice at start of treatment at the early stages of glaucoma, and in 33.82 % — at terminal stages of glaucoma. Quantity of combined drugs prescriptions at the start of treatment was significantly increased if the stage of the disease was more complex. At the early and advanced stages of glaucoma prostaglandin analogues were administered up to the end of treatment in 17 % and 19 % of cases respectively, and this figure is statistically significantly exceeded the quantity of prescriptions at the start of treatment. Monotherapy is not always effective or sufficiently effective. Thus, 27–33 % of patients suffering from glaucoma or ophthalmic hypertension, require additional lowering IOP immediately after start of treatment, and more than half of patients receiving β-blockers, by the end of the second year of require correction treatment due to lack of hypotensive effect [12].

Furthermore, all effective antihypertensive drugs have one or another side effect [7]. In case of

inefficiency or lack of effectiveness of drugs chosen to achieve the desired pressure values, or progression of the disease, it is necessary to switch to the combination therapy. When applying the combination therapy, no more than two drugs, belonging to different pharmacological groups, must be used simultaneously. Combinations of substances, having differently directed action (reduction of the intraocular fluid production and increasing of its outflow) lead to an additive effect, which manifests itself in a marked reduction in IOP compared with monotherapy by means of each medicine separately [22]. At the same time, for higher effectiveness of glaucoma treatment and improving quality of patients' life, it is preferable to use the drugs in a form of fixed combinations [12, 17, 22].

Currently 43 drugs are registered in Ukraine, that cover all pharmacological groups of drugs for antihypertensive therapy of glaucoma and in 95 % cases they are used locally. Out of these, 13 drugs or third part constitute mono-drugs on basis of timolol, 9 drugs are combined drugs that include timolol as one of the pharmaceutical substances, 10 are mono-drugs, that are manufactured by domestic pharmaceutical enterprises [6].

Because of changed conceptions about the nature of the disease and its pathogenesis, recently neuroprotective glaucoma therapy has become increasingly important [4, 10, 13, 19, 17]. Mostly, normalization of IOP is ineffective because of absence in combined treatment of drugs having neuroprotective action [2, 11, 13], so that even after lowering and normalization of IOP process of glaucomatous optic nerve atrophy does not stop immediately [11, 16]. Neuroprotective glaucoma therapy is aimed primarily at correcting metabolic disorders occurring at glaucoma in optic nerve, improvement of local microcirculation and tissues trophism, normalization of blood rheology, increase of blood flow. Neuroprotectors of direct action directly protect neurons in the retina and optic nerve fibers by blocking factors directly damaging cells that cause increase in concentration of lipid peroxidation products (LPO) and free radicals, calcium, acidosis [13, 17]. Effects of NMDA-receptor blockers (remacemide, magnesia, glycine, eliprodil, memantin and so on [13, 17]) and antagonists of voltage-dependent calcium channels (betaxolol, amlodipine, nifedipine, and so on [2, 17]) are aimed at interrupting of the ischemic cascade earliest processes. All the listed drugs, save for betaxolol, are used orally or parenterally. Given the fact that neuroprotective treatment of GON must be prescribed to patients with glaucoma constantly, drugs that have no contraindications and are able to act preventively become especially needed [17]. From this point of view, the most promising is use of secondary neuroprotectors, which are aimed at interruption of delayed neuronal death mechanisms, namely peptide bioregulators (cortexin, retinalamin [13, 16, 17]) and antioxidants (superoxide dismutase, histochrom, mexidol, vitamins A, E, B1, B2, B6 and B12, ascorbic acid, emoxipinum, lipoic acid, thiotriasoline, taurine, lipoflavon and so on [2, 4, 10, 13, 17, 20-25, 28]).

It should be noted, that free-radical processes play important role in pathogenesis of glaucoma [3, 29]. In these cases content of active oxygen forms in eye tissues and fluids increases, and activity of its own antioxidant system decreases, resulting in activation of lipid peroxidation. Thus, degenerative processes in tissues of the drainage system occur at abnormally high concentrations of active pro-oxidant in intraocular fluid and at reduced activity of its own antioxidant system, leading to decreased permeability of these tissues and reduced outflow of intraocular fluid [3]. Chronic hypoxia in which the optic nerve dwells at glaucoma, also leads to increased production of active forms of oxygen, lipid peroxidation, damage intracellular membranes and, ultimately, death of nerve cells [19, 29]. Given angioprotective properties of antioxidants and their ability to reduce permeability of blood vessels, improve microcirculation and tissue metabolism, protect retina from harmful action of light, promote regeneration of damaged tissues and resorption of intraocular hemorrhage, which is also important from the point of view of long-term use of drugs, application of antioxidants is justified and indicated for treatment of glaucoma.

Among the promising directions there is also combined therapy with antihypertensive drugs that include substances, which on one hand potentiate the anti-glaucomatous effect, and on the other improve dynamics of vision field. For this purpose, it is proposed to apply preliminary instillation of carbonic anhydrase inhibitors, antiadrenergic or combined drugs (for example proxodolol, timolol, trusopt, proxofeline) followed by administration into eye of emoxipinum or taurine [9, 23].

Another area to which one should pay attention is side effects caused by regular use of drugs. These comorbidities include development of «dry eye» (DES) syndrome, which is triggered by polyetiological nature of corneal xerosis [1, 26]. Long-term antihypertensive therapy which success is connected with instability of lachrymal film, causes visual fatigue, affects the refractive properties of eye, limiting working capacity of patients, forces to use increasing number of drugs (therapy of glaucoma as well as DES), causes discomfort when using

mono-drugs, and eventually decreases the effectiveness of glaucoma treatment. To solve this problem, firstly it is necessary to develop drugs with a low content of preservatives («Nyolol®», Novartis Pharma AG, «Arutimol®», Chauvin ankerpharm GmbH), affecting disorder in formation and preservation of lachrymal film, or completely exclude them from the medicines («Taflotan®», Santen Oy) [1, 27]. Secondly, the drug composition includes components, that provide additional moistening of eye in case of own tear-producing structures insufficiency, and gel formulations that promote conservation of tear components on the eye surface and ensure stability of lachrymal film, for example, hyaluronic acid, povinilpirolidon, carbopol («Nyolol®», «Arutimol®») [1].

CONCLUSIONS AND RECOMMENDATIONS FOR FURTHER RESEARCH

The above indicates relevance of the research aimed at developing combined eye drops having anti-glaucomatous action, which are currently one of the most common and easy-to-use formulations among all eye medications. Combining of substances, which influence various chains of pathogenesis, and, specifically, antihypertensive drugs and substances that enhance their performance through some other mechanism, and also have neuroprotective properties, and creation on their basis of an effective drug in conjunction with minimal quantity of side effects, will promote optimization of glaucoma modern therapy.

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УДК 615.457.07

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ОБҐРУНТУВАННЯ СТВОРЕННЯ КОМБІНОВАНОГО ПРЕПАРАТУ ДЛЯ ТЕРАПІЇ ГЛАУКОМИ ЯК ОДИН З ЕЛЕМЕНТІВ ЦІЛЬОВОГО ПРОФІЛЮ ЯКОСТІ ЛІКАРСЬКОГО ЗАСОБУ

З метою визначення одного з елементів цільового профілю якості препарату (передбачуване застосування у клінічних умовах, шлях введення, лікарська форма, сила дії дози) проведено пошук і аналіз сучасної інформації щодо патогенезу, методів лікування і готових лікарських засобів для лікування глаукоми. Проведені дослідження дозволили обґрунтувати актуальність та перспективність напрямків у комбінуванні лікарських засобів, що впливають на різні ланцюги патогенезу, та створення на їх основі ефективного препарату у формі очних крапель, який сприятиме оптимізації сучасної терапії глаукоми.

Ключові слова: глаукома, внутрішньоочний тиск, незворотна сліпота, гіпотензивна терапія, комбіновані препарати, перекисне окиснення ліпідів.

УДК 615.457.07

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ОБОСНОВАНИЕ СОЗДАНИЯ КОМБИНИРОВАННОГО ПРЕПАРАТА ДЛЯ ТЕРАПИИ ГЛАУКОМЫ КАК ОДИН ИЗ ЭЛЕМЕНТОВ ЦЕЛЕВОГО ПРОФИЛЯ КАЧЕСТВА ЛЕКАРСТВЕННОГО СРЕДСТВА

С целью определения одного из элементов целевого профиля качества препарата (предсказуемое применение в клинических условиях, путь введения, лекарственная форма, сила действия дозы) проведен поиск и анализ современной информации о патогенезе, методах лечения и готовых лекарственных средствах для лечения глаукомы. Проведенные исследования позволили обосновать актуальность и перспективность направлений в комбинировании лекарственных средств, влияющих на различные цепи патогенеза, и создание на их основе эффективного препарата в форме глазных капель, который будет способствовать оптимизации современной терапии глаукомы.

Ключевые слова: глаукома, внутриглазное давление, необратимая слепота, гипотензивная терапия, комбинированные препараты, перекисное окисление липидов.

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Надійшла до редакції:
16.08.2013