UDC: 615.457:615.31`792]:617.7-001-085].012

Experimental evaluation of the specific activity of the new Angiolin dosage form in the research corneal burn's condition

I. F. Bielenichev*[1,A,E], L. I. Kucherenko[1,2,F], I. A. Mazur[1,2,F,E], R. R. Akopian[1,B,C,D], O. V. Khromylova[1,E], I. V. Pavliuk[3,E]

[1]Zaporizhzhia State Medical University, Ukraine, [2]SPA "Farmatron", Zaporizhzhia, Ukraine, [3]Zaporizhzhia Research Experimental Forensic Center of the Ministry of Internal Affairs of Ukraine

A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

Visual organ injuries are still one of the main causes of blindness and occupational disability. Despite the good protection of the eyeball by the bone walls of the orbit and adnexa oculi, its injuries are 5–10 % of the total number of all damages in peacetime and about 20 % in wartime. Employees of the Department of Pharmaceutical Chemistry of Zaporizhzhia State Medical University (ZSMU) together with the specialists of the SPA "Farmatron" under the supervision of professor I. A. Mazur synthesized a new compound, called Angiolin.

The aim of the research is to study the anti-inflammatory, wound-healing, reparative activity of the Angiolin eye drops action during a chemical burn of the cornea rabbits modeling.

Materials and methods. The pharmacological efficacy of the prepared Angiolin eye drops in concentrations: 0.5 %, 1.0 %, 1.5 %, 2.0 % and 2.5 % has been studied. All studies were carried out on 40 eyes of 20 Chinchilla breed rabbits of both sexes weighing 2.1–3.5 kg. The chemical burn model was reproduced according to the Obenberger method using 10 % sodium hydroxide solution (application of 8 mm blotting paper), exposure time 20 seconds, after preliminary installation anesthesia with 0.5 % Alcaine solution.

Results. Based on experimental data, it can be noted that Angiolin eye drops in concentrations: 1.0 %, 1.5 %, 2.0 %, 2.5 % show almost the same pharmacological activity, and 1 % Angiolin eye drops were the most effective, that gives us the opportunity for further study.

Conclusions. Angiolin eye drops exhibit high anti-inflammatory, wound healing, reparative activity in the treatment of eye burn. As a result of the study, it was found that 1 % of Angiolin eye drops turned out to be the most effective. The obtained results are an experimental rationale for further study of 1 % Angiolin eye drops.

Key words: (S)-2,6-diaminohexanoic acid 3-methyl-1,2,4-triazolyl-5-thioacetate, thiotriazoline.

Zaporozhye medical journal 2019; 21 (6), 815–819

DOI: 10.14739/2310-1210.2019.6.186626

***E-mail:** i.belenichev1914@gmail.com

Експериментальне оцінювання специфічної активності нової лікарської форми Ангіолін в умовах хімічного опіку рогівки

І. Ф. Бєленічев, Л. І. Кучеренко, І. А. Мазур, Р. Р. Акопян, О. В. Хромильова, І. В. Павлюк

Пошкодження органу зору залишаються однією з основних причин сліпоти та професійної інвалідності. Незважаючи на захищеність очного яблука кістковими стінками орбіти та придатками ока, його пошкодження становлять 5–10 % від загальної кількості всіх травм у мирний час і майже 20 % у воєнний. Співробітники кафедри фармацевтичної хімії Запорізького державного медичного університету (ЗДМУ) спільно з фахівцями НВО «Фарматрон» під керівництвом професора І. А. Мазура синтезували нову сполуку, що отримала назву Ангіолін.

Мета роботи – дослідження протизапальної, ранозагоювальної, репаративної дії очних крапель Ангіолін під час моделювання хімічного опіку рогівки очей кроликів.

Матеріали та методи. Вивчили фармакологічну ефективність приготованих очних крапель Ангіолін у концентраціях 0,5 %, 1 %, 1,5 %, 2,0 % і 2,5 %. Усі дослідження виконали на 40 очах 20 кроликів породи шиншила обох статей масою 2,1–3,5 кг. Модель хімічного опіку відтворена за методом Обенберґера за допомогою 10 % розчину натрію гідроксиду (аплікацією 8 мм кола фільтрувального паперу), час експозиції – 20 секунд після попередньої інсталяційної анестезії 0,5 % розчином алкаїна.

Результати. Виходячи з експериментальних даних, очні краплі Ангіолін у концентраціях 1,0 %, 1,5 %, 2,0 %, 2,5 % виявляють майже однакову фармакологічну активність, а найбільш ефективними виявилися 1 % очні краплі Ангіолін, що зумовлює перспективність продовження їх вивчення.

Висновки. Очні краплі Ангіолін виявляють високу протизапальну, ранозагоювальну, репаративну активність під час лікування опіків очей. У результаті досліджень встановили, що найбільш ефективними виявилися 1 % очні краплі Ангіолін. Результати є експериментальним обґрунтуванням дальшого вивчення 1 % очних крапель Ангіолін.

Ключові слова: (S)-2,6-диаміногексанової кислоти 3-метил-1,2,4-триазоліл-5-тіоацетат, тіотриазолін.

Запорізький медичний журнал. – 2019. – Т. 21, № 6(117). – С. 815–819

Экспериментальная оценка специфической активности новой лекарственной формы Ангиолин в условиях химического ожога роговицы

И. Ф. Беленичев, Л. И. Кучеренко, И. А. Мазур, Р. Р. Акопян, О. В. Хромылёва, И. В. Павлюк

Повреждения органа зрения остаются одной из основных причин слепоты и профессиональной инвалидности. Несмотря на хорошую защищенность глазного яблока костными стенками орбиты и придатками глаза, его повреждения составляют

Ключевые слова: (S)-2,6-диаминогексановой кислоты 3-метил-1,2,4-триазолил-5-тиоацетат, тиотриазолин.

Запорожский медицинский журнал. – 2019. – Т. 21, № 6(117). – С. 815–819

5–10 % от общего количества всех травм в мирное время и около 20 % в военное. Сотрудники кафедры фармацевтической химии Запорожского государственного медицинского университета (ЗГМУ) совместно со специалистами НПО «Фарматрон» под руководством профессора И. А. Мазура синтезировали новое соединение, получившее название Ангиолин.

Цель работы – изучить противовоспалительное, ранозаживляющее, репаративное действие глазных капель Ангиолин при моделировании химического ожога роговицы глаз кроликов.

Материалы и методы. Изучили фармакологическую эффективность приготовленных глазных капель Ангиолин в концентрациях 0,5 %, 1,0 %, 1,5 %, 2,0 % и 2,5 %. Все исследования выполнены на 40 глазах 20 кроликов породы шиншилла обоих полов массой 2,1–3,5 кг. Модель химического ожога воспроизведена по методу Обенбергера при помощи 10 % раствора натрия гидроксида (аппликацией 8 мм круга фильтровальной бумаги), время экспозиции – 20 секунд после предварительной инсталляционной анестезии 0,5 % раствором алкаина.

Результаты. Исходя из экспериментальных данных, глазные капли Ангиолин в концентрациях 1,0 %, 1,5 %, 2,0 %, 2,5 % проявляют практически одинаковую фармакологическую активность, а наиболее эффективными оказались 1 % глазные капли Ангиолин, что обусловливает перспективность их дальнейшего изучения.

Выводы. Глазные капли Ангиолин проявляют высокую противовоспалительную, ранозаживляющую, репаративную активность при лечении ожогов глаз. В результате исследований установили, что наиболее эффективными оказались 1 % глазные капли Ангиолин. Результаты являются экспериментальным обоснованием для дальнейшего изучения 1 % глазных капель Ангиолин.

Visual organ injuries are still one of the main causes of blindness and occupational disability. Despite the good protection of the eyeball by the bone walls of the orbit and adnexa oculi, its injuries are 5–10 % of the total number of all damages in peacetime and about 20 % in wartime [4,6,7].

Nearly 20 % of the entire eye pathology is injuries; they are the cause of unilateral blindness in 50 % of cases, bilateral – 20 %. Eye injuries are observed mainly in people of the most working age (84.6 % at 20–30 years old) and often lead to restriction or total loss of working ability, and the state suffers significant economic damage – in almost half of cases, victims are released from work for at least 3–7 days. Visual organ injuries are divided into mechanical (damages) and burns.

Injuries, in turn, are divided into contusions and wounds. Contusions are inflicted by blunt objects (fist, snowball, clod of earth, stone, etc.), and wounds – by sharp, prickly, or cutting objects (knife, scissors, needle, nail, etc.). Contusions predominantly cause damage to all parts of the visual organs, but they are conventionally divided into adnexa oculi contusions and eyeball contusions. Wounds are also divided into adnexa oculi wounds and eyeball wounds. Eyeball wounds, in turn, are divided into penetrating and nonpenetrating. Penetrating eyeball wounds can be without and with the intraocular foreign bodies [5].

Among all visual organ injuries, eye burns are one of the most serious clinical and social problems and are second in severity after penetrating wounds in the structure of visual organ injuries and are recorded in 20.0–42.2 % of cases. The main component of the adult population with this pathology (up to 70 %) is a person of working age, at the age of 19–45 years (63 %), mostly male (78 %). In connection with the crime situation that has been created, as well as the ATO in the South-East of the country, the number of visual organ injuries has sharply increased, among which contusion and burn injury came out on top and are noted in 50–64 % of cases. Chemical eye burns are one of the most severe types of visual organ injuries, both in the nature of changes in the tissues and in the outcome. The pathological mechanism of burn disease and its consequences is multifactorial. According to the literature data, corneal epithelium membranes are destroyed by chemical burns; its architectonics, chemical property, all types of metabolism are disturbed; the systemic changes also occur in the body (kidney failure, liver dysfunction, dyspancreatism). In addition, burn injury creates favorable conditions for the development of a secondary infection, which increases intoxication and aggravates the burn [3].

For many years, the studies have been conducted on the conservative treatment of hemorrhage in various parts of the eye, searching for the most effective and safe drugs, studying the methods and doses of their use, improving the regimen of resolution therapy [5].

In the early 90s of the last century, free-radical links of oxidative stress drew the attention of pharmacologists and clinicians as a target of drug treatment of eye contusional injuries. Hyperproduction of the reactive oxygen species and NO neurochemical reactions (transmitter autocoidosis) and IL-1b-induced iNO Shyperexpression leads to oxidative modification of receptor protein structures, ion channels, cell membranes of the visual analyzer, impaired photochemical reactions, suppression of nerve impulses generation and conduction, reduced vision, and blindness. As a rule, such disorders occur against the background of deprivation of the expression of the antioxidant system that control photochemical reactions in the retina. Thus, a decrease in the expression of Se-GPR mRNA and its activity was detected in patients with contusional lesions of the eye membranes. At this time, emoxipin, mexidol, thiotriazoline, cysteine, succinic acid salts, etc., became widely used as water-soluble antioxidants in ophthalmic practice. However, the effectiveness of antioxidants does not always

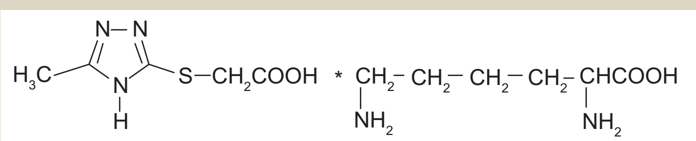

Fig. 1. The structural formula of Angiolin ((S)-2,6-diaminohexanoic acid 3-methyl-1,2,4-triazolyl-5-thioacetate).

meet the requirements of ophthalmologists, because their mechanism of action does not affect the initial and primary stages of the molecular-biochemical cascade of damage to the eye membranes during contusion [1,2].

In relation to revolutionary discoveries in neurobiology, neurochemistry, and neurophysiology and the disclosure of the role of glutamate excitotoxicity, neuroapoptosis trigger mechanisms, molecular factors of endogenous neuroprotection, the question of including of neuroprotectors in the complex therapy of contusional injuries of the eye was recently discussed. The main direction of neuroprotection in case of eye injury is the reduction of excitotoxicity (magnesium ions and glycine), energy deficiency (succinic acid salts, thiotriazoline), ROS/NO-dependent mechanisms of neurodestruction (thiotriazoline, mexidol, ergotein, emoxipin, glutathione, cysteine). The drugs that inhibit neuroapoptosis (recombinant drugs of the anti-apoptic protein bcl-2) are of some interest. In addition, the promising use of the following drugs is considered: modulators of endogenous neuroprotection, in particular regulators of the expression of the heat shock protein 70 kDa -HSP70 (selective modulators of estrogen receptors, intermediates of the glutathione system – selenase, glutaredoxin, glutathione, melatonin). In this regard, special attention is attracted by the new original drug – Angiolin [1,9].

The employees of the Department of Pharmaceutical Chemistry of Zaporizhzhia State Medical University (ZSMU) together with the specialists of the SPA "Farmatron" under the supervision of professor I. A. Mazur synthesized a new compound, called Angiolin.

Therefore, it is advisable to expand the range of domestic medicines, namely, eye drops with wound healing, reparative, anti-inflammatory, and local anesthetic actions, in order to improve the therapeutic effect and cost-effectiveness of treatment.

The aim

The aim of the research is to study the anti-inflammatory, wound-healing, reparative activity of the Angiolin eye drops action during a chemical burn of the cornea rabbits modeling.

Materials and methods

In the course of work in the Drug Standardization and Formulation Laboratory of the Department of Pharmaceutical Chemistry, ZSMU, Angiolin eye drops were made in the following concentrations: 0.5 %, 1.0 %, 1.5 %, 2.0 % and 2.5 % (used series: Angiolin, experimental series 9, produced by the State Enterprise "Chemical Reagents Plant" of the Scientific and Technical Complex "Institute of Single Crystals" of the National Academy of Sciences of Ukraine) [8,9].

We have studied the pharmacological efficacy of the prepared Angiolin eye drops in concentrations: 0.5 %, 1.0 %, 1.5 %, 2.0 % and 2.5 %.

All studies were carried out on 40 eyes of 20 Chinchilla breed rabbits of both sexes weighing 2.1–3.5 kg. The chemical burn model was reproduced according to the Obenberger method using 10 % sodium hydroxide solution (application of 8 mm blotting paper), exposure time 20 seconds, after preliminary installation anesthesia with 0.5 % Alcaine solution. From the first day, rabbits have administrated 0,1 ml of eye drops 3 times a day for 14 days into the conjunctiva. 0.5 %, 1.0 %, 1.5 %, 2.0 % and 2.5 % Angiolin drops were used. The rabbits of the control group were administrated with the same volume of saline. There were 5 rabbits in each group. From the first day of the experiment, an ophthalmoscopic examination of animals was made. We have also determined the signs of corneal syndrome – (lacrimation, photophobia, pain during villus irritation, blepharospasm), as well as chemosis, areas of ischemia and superficial necrosis of the conjunctiva, dilation of blood vessels and limb edema in points, which are assigned depending on the severity of edema, hyperemia, erosion: 0 points – the sign is absent, 1 point – the sign is expressed slightly, 2 points – the sign is expressed moderately, 3 points – the sign is expressed strongly. Corneal defects were measured quantitatively (diameter using caliper).

The study results were processed using the statistical package of the licensed program Statistica® for Windows 6.0 (StatSoft Inc., No. AXXR712D833214FAN5), as well as SPSS 16.0, and Microsoft Excel 2003. Separate statistical procedures and algorithms are implemented as specially written macros in the corresponding programs. For all types of analysis, the differences were considered statistically significant at $P < 0.05$.

Results

In groups of animals treated with Angiolin, on the 2nd day of treatment, the cornea was available for inspection. The reduction of the epithelium defect in the form of a circle to 3.35 mm and 2.11 mm by the end of the 14th day was determined. It is worth noting that in groups of animals that received 1.0 %, 1.5 %, 2.0 % and 2.5 % Angiolin eye drops, epithelization proceeded faster, with its full completion on the 8–11 days.

Table 1. The clinical status of the rabbits' eyes on the 14th day after the burn injury and treatment with Angiolin eye drops (in points)

Animal groups	Photophobia	Blepharospasm	Hyperemia	Lacrimation	Corneal defect, mm
Intact (n = 5)	0	0	0	0	–
Burn (control) (n = 5)	3	3	3	3	6.73 ± 0.41
Angiolin, 0,5 % (n = 5)	1.20 ± 0.44	1	1.80 ± 0.44	1.80 ± 0.44	3.35 ± 0.54* (-50.2 %)
Angiolin, 1 % (n = 5)	1	1	1	1	2.41 ± 0.31* (-64.1 %)
Angiolin, 1.5 % (n = 5)	1	1	1	1	2.47 ± 0.27* (-63.3 %)
Angiolin, 2.0 % (n = 5)	1	1	1	1	2.45 ± 0.22* (-63.6 %)
Angiolin, 2.5 % (n = 5)	1	1	1	1	2.48 ± 0.27* (-63.1 %)

0 points: no sign, **1 point:** expressed slightly sign, **2 points:** moderately expressed sign, **3 points:** strongly expressed sign;*: $P < 0.05$ in relation to control.

Thus, it can be noted that eye drops containing Angiolin as an active ingredient exhibit a high anti-inflammatory, wound-healing, reparative activity in the treatment of eye burns.

In addition, based on experimental data (*Table 1*), it can be noted that Angiolin eye drops in concentrations: 1.0 %, 1.5 %, 2.0 %, 2.5 % show almost the same pharmacological activity, and the most effective were 1 % Angiolin eye drops, that gives us the opportunity to conduct further study. The mechanism of therapeutic action of Angiolin eye drops is associated with its chemical structure. Thus, the L-lysine residue is also metabolized into pipecolic acid, which enhances the affinity of the GABA-benzodiazepin receptor complex. This effect of lysine is especially important in conditions of glutamate "excitotoxicity", which occurs in hypoxia and leads to an increase in intracellular Ca^{2+} concentration, activation of NO synthase, intensive formation of NO and peroxynitrite ($ONOO^-$), which is the immediate cause of cell death. By enhancing the affinity of GABA receptors, pipecolic acid reduces the hyperexcitability of glutamate receptors, the release of exciting amino acids (glutamate and aspartate) and, thereby, neutralizing manifestations of glutamate "excitotoxicity" [10].

Another important effect of L-lysine is its ability to replace arginine in nitric oxide synthesis reactions, which also leads to a decrease in the manifestations of nitrosative stress in the nervous tissue in hypoxia [11].

Discussion

The significant antioxidant activity of Angiolin is due to the presence of a thiol group in its structure. Thereby the drug has pronounced reparative properties and the ability to receive electrons from various reactive oxygen species. In this case, sulfur in the thiol groups passes from bi- to the tetravalent state. Proceeding from the above, Angiolin can be attributed to the group of antioxidants, which are the "traps" of free radicals. This group of medicines converts oxygen free radicals to an inactive state, promotes reactivation of antioxidant enzymes, and contributes to more efficient use of the non-enzymatic tocopherol antioxidant [12].

During course administration, Angiolin is known to increase the concentration of HSP_{70} protein in damaged nerve tissue [13], which may be a key mechanism of its protective action in corneal burns. HSP proteins are induced in the cells of all living organisms in response to the action of numerous stressors, such as heat shock, hypoxia, ischemia, metabolic disorders, viral infection and pharmacological agents' influence [10]. The genes of these proteins are activated not only under stress, but also during the main processes of cellular activity, proliferation, differentiation, and apoptosis. HSPs take part in all vital processes of tissues and organs [14,15].

Thus, the creation of eye drops based on the original drug Angiolin, which exhibits antioxidant, neuroprotective, mitoprotective properties and is able to regulate HSP_{70} expression, can optimize approaches to the complex treatment of corneal chemical burn.

Conclusions

1. Angiolin eye drops exhibit high anti-inflammatory, wound healing, reparative activity in the treatment of eye burns.

2. As a result of the study, it was found that 1 % of Angiolin eye drops turned out to be the most effective.

3. The obtained results are an experimental rationale for further study of 1 % Angiolin eye drops.

Conflicts of interest: authors have no conflict of interest to declare.
Конфлікт інтересів: відсутній.

Надійшла до редакції / Received: 06.05.2019
Після доопрацювання / Revised: 14.06.2019
Прийнято до друку / Accepted: 27.06.2019

Information about authors:
Bielenichev I. F., PhD, Dr.hab., Professor, Head of the Department of Pharmacology and Medical Formulation, Zaporizhzhia State Medical University, Ukraine.
Kucherenko L. I., PhD, Dr.hab., Professor, Head of the Department of Pharmaceutical Chemistry, Zaporizhzhia State Medical University, Vice-President of SPA "Farmatron", Zaporizhzhia, Ukraine.
Mazur I. A., PhD, Dr.hab., Professor, Zaporizhzhia State Medical University, President of SPA "Farmatron", Zaporizhzhia, Ukraine.
Akopian R. R., Postgraduate Student of the Department of Pharmaceutical Chemistry, Zaporizhzhia State Medical University, Ukraine.
Khromylova O. V., PhD, Associate Professor of the Department of Pharmaceutical Chemistry, Zaporizhzhia State Medical University, Ukraine.
Pavliuk I. V., PhD, Senior Judicial Expert in the Sector for the Study of Narcotic Drugs, Psychotropic Substances, their Analogues and Precursors in the Materials and Products Research Division, Zaporizhzhia Research Experimental Forensic Center of the Ministry of Internal Affairs of Ukraine.

Відомості про авторів:
Бєленічев І. Ф., д-р біол. наук, професор, зав. каф. фармакології та медичної рецептури, Запорізький державний медичний університет, Україна.
Кучеренко Л. І., д-р фарм. наук, професор, зав. каф. фармацевтичної хімії, Запорізький державний медичний університет, віце-президент НВО «Фарматрон», м. Запоріжжя, Україна.
Мазур І. А., д-р фарм. наук, професор, Запорізький державний медичний університет, президент НВО «Фарматрон», м. Запоріжжя, Україна.
Акопян Р. Р., очний аспірант каф. фармацевтичної хімії, Запорізький державний медичний університет, Україна.
Хромильова О. В., канд. фарм. наук, доцент каф. фармацевтичної хімії, Запорізький державний медичний університет, Україна.
Павлюк І. В., канд. біол. наук, старший судовий експерт сектора дослідження наркотичних засобів, психотропних речовин, їх аналогів і прекурсорів відділу досліджень матеріалів і виробів, Запорізький науково-дослідний експертно-криміналістичний центр МВС України.

Сведения об авторах:
Беленичев И.Ф., д-р биол. наук, профессор, зав. каф. фармакологии и медицинской рецептуры, Запорожский государственный медицинский университет, Украина.
Кучеренко Л. И., д-р фарм. наук, профессор, зав. каф. фармацевтической химии, Запорожский государственный медицинский университет, вице-президент НПО «Фарматрон», г. Запорожье, Украина.
Мазур И. А., д-р фарм. наук, профессор, Запорожский государственный медицинский университет, президент НПО «Фарматрон», г. Запорожье, Украина.
Акопян Р. Р., очный аспирант каф. фармацевтической химии, Запорожский государственный медицинский университет, Украина.

Хромылева О. В., канд. фарм. наук, доцент
каф. фармацевтической химии, Запорожский государственный медицинский университет, Украина.
Павлюк И. В., канд. биол. наук, старший судебный эксперт сектора исследования наркотических средств, психотропных веществ, их аналогов и прекурсоров отдела исследований материалов и изделий Запорожского научно-исследовательского экспертно-криминалистического центра МВД Украины.

References

[1] Belenichev, I. F., Mazur, I. A., Kucherenko, L. I., Nagornaya, E. A., Gorbacheva, S. V., & Bidnenko, A. S. (2016). The molecular and ultrastructural aspects of the formation of mitochondrial dysfunction in the modeling of chronic cerebral ischemia: The mitoprotective effects of Angiolin. *Neurochemical Journal,* 10(2), 131-136. doi: 10.1134/s1819712416010025
[2] Kucherenko, L. I., Hromyleva, O. V., Mazur, I. A., & Shishkina, S. V. (2017). Theoretical study about L-arginine complexes formation with thiotriazolin. *Zaporozhye medical journal*, 19(1), 108-112. doi: 10.14739/2310-1210.2017.1.91736
[3] Chekman, I. S., Kazakova, O. O., Mazur, I. A., Nahorna, O. O., Bielenichev, I. F., & Horchakova, N. O. et al. (2017). Novyi oryhinalnyi metabolitotropnyi endotelioprotektor “Angiolin”: kvantovo-khimichni parametry ta osoblyvosti farmakolohichnoi dii [New original metabolitotropic endothelioprotector “Angiolin”: quantum-chemical parameters and peculiarities of pharmacological action]. *Reports Of The National Academy Of Sciences Of Ukraine,* 8, 86-93. doi: 10.15407/dopovidi2017.08.086 [in Ukrainian]
[4] Kolesnik, Yu. M., Chekman, I. S., Mazur, I. A., Bielenichev, I. F., Horchakova, N. A. & Nahorna, O. O. (2014). Mekhanizmy rozvytku endotelialnoi dysfunktsii ta poshuk endotelioprotektoriv [Mechanisms of development of endothelial dysfunction and search for endothelioprotectors]. *Journal of the National academy of medical sciences of Ukraine,* 20(3), 289-299. [in Ukrainian].
[5] Gladunova, E. P., Shirolapova, A. Ju., & Kurkin, V. A. (2015). Sovershenstvovanie obespechenija naselenija kontroliruemymi gruppami lekarstvennyh preparatov [Improving the provision of the population with controlled drug groups]. *Pharmacy*, 2, 32-36. [in Russian].
[6] Mashkovskij, M. D. (2012). *Lekarstvennye sredstva [Drugs].* (16th ed.) Moscow. [in Russian].
[7] Chekman, I. S., Nebesna, T. Yu., Kazakova, O. O., & Simonov, P. V. (2010). Farmakofory: stvorennia likarskykh zasobiv [Pharmacophores: the creation of medicines]. *Journal of the Academy of Medical Sciences of Ukraine, 16(3),* 424-437.[in Ukrainian].
[8] Kucherenko, L. I., Belenichev, I. F. & Bidnenko, A. S., (2015). Angiolin – novyj predstavitel metabolitotropnyh preparatov s vyrazhennym vlijaniem na jendotelij sosudov golovnogo mozga i serdca [Angiolin – is an ewrepresentative of metabolitotropic drugs with pronounced effect on the vascular endothelium of the brain and heart]. *MHO Inter-Medical,* 4(10), 11-14. [in Russian].
[9] Bidnenko, O. S. (2014). Shchodo tekhnolohii vyrobnytstva substantsii “Lizynii” [As for the technology of production of the substance “Lysine”]. *Modern aspects of medicine and pharmacy.* Proceedings of the Scientific and Practical Conference, (p. 163). Zaporizhzhia. [in Ukrainian].
[10] Khurana, A. K., Khurana, Aruj K. & Khurana, B. (Eds.). (2015). *Review of Ophthalmology.* (6th ed.). India: Jaypee Brothers Medical Publishers (Verlag).
[11] Khurana, A. K., Khurana, Aruj K. &Khurana, B. (Eds.). (2015). *Comprehensive Ophthalmology.*(6th ed.). New Delhi: Jaypee Brothers Medical Publishers (Verlag).
[12] Purdy, E. P. (Ed.). (2012). *Basic and Clinical Science Course. Section 1: Update on General Medicine*. Canada: American Academy of Ophthalmology.
[13] Chalam, K. V. (Ed.). (2012). *Basic and Clinical Science Course. Section 2: Fundamentals and Principles of Ophthalmology*. Canada: American Academy of Ophthalmology.
[14] Raab, E. L. (Ed.). (2012). *Basic and Clinical Science Course. Section 6: Pediatric Ophthalmology and Strabismus*. Canada: American Academy of Ophthalmology.
[15] Holds, J. B. (Ed.). (2012). *Basic and Clinical Science Course. Section 7: Orbit, Eyelids, and Lacrimal System*. Canada: American Academy of Ophthalmology.