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SUBSTANTIATION OF THE ETHIOPATHOGENIC CHOICE OF SUBSTITUTION THERAPY MEDICATIONS FOR THE DRY EYE SYNDROME

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Ключевые слова: *синдром сухого глаза, средства заместительной терапии, этиопатогенетическое лечение*

Abstract. Substantiation of the ethiopathogenic choice of substitution therapy medications for the dry eye syndrome. Kryvoviaz O.V., Tomashevska Yu.O., Makarenko O.V., Kudria V.V. *The purpose of the study is to substantiate the personalized selection of substitution therapy medications with the consideration of the pathogenesis of dry eye syndrome development in each patient. In order to achieve the set goal, we conducted a content-analysis of the*

information from nomenclature on active ingredient as well as on the mechanisms of action of substitution therapy medications provided in the prescribing information and labeling of the medications. After that, we performed a pathogenetic ranging of substitution therapy medications depending on the way they influence a certain aspect of disorder of the tear film renewal process in dry eye syndrome. The information received in the course of the conducted research makes it possible for an ophthalmologist – basing on information on the disorder in the quantitative and qualitative correlation between the tear film layers received with the help of modern diagnostic tools to prescribe targeted dry eye syndrome treatment taking into account the necessary point of application of the substitution therapy medications, considering their composition and action mechanism of the active ingredients which they contain.

Реферат. Обґрунтування етіопатогенетичного вибору засобів замісної терапії синдрому сухого ока. Кривов'яз О.В., Томашевська Ю.О., Макаренко О.В., Кудря В.В. *Метою роботи стало обґрунтування індивідуалізованого вибору засобів замісної терапії з урахуванням патогенезу розвитку синдрому сухого ока в кожного окремого пацієнта. Для досягнення поставленої мети було здійснено контент-аналіз інформації з номенклатури активних інгредієнтів та механізмів дії засобів замісної терапії, наведеної в інструкціях для медичного застосування лікарського засобу, інструкціях з використання медичного виробу та інструкціях із застосування. Наступним етапом роботи було здійснене патогенетичне ранжування ЗЗТ залежно від їх впливу на певну ланку порушення процесу оновлення слізної плівки при синдромі сухого ока. Отримана в результаті проведеного дослідження інформація дає можливість лікарю-офтальмологу, базуючись на результатах порушення кількісного та якісного співвідношення шарів слізної плівки, отриманих за допомогою новітніх засобів діагностики, прицільно здійснювати лікування синдрому сухого ока з урахуванням необхідної точки прикладання дії засобів замісної терапії, зважаючи на вміст та механізм дії активних інгредієнтів у них.*

The international medical and pharmaceutical community notice the increased influence of the diseases of civilization on people's health and quality of life. Particularly, the dry eye syndrome (DES) has become especially important over the last decade [4, 5, 8]. This is proved by the data on the spread of the stated pathology. Thus, it is noted that 10-30% of laboring population suffer from DES. In addition, about 75% of the patients who visit an ophthalmologist, claim to have at least some symptoms of this syndrome [7]. Moreover, the establishment and active work of the working groups with the participation of health care specialists from all continents also confirm the increasing level of specialists' interest [5, 6, 7, 8, 9, 10].

According to the definition, adopted at the 2017 International Dry Eye Workshop II in 2017, DES is characterized by a loss of homeostasis of the tear film (TF), and accompanied by ocular symptoms, in which tear film instability plays an etiological role [5]. Ukraine is no exception.

Despite the spread of DES in ophthalmological patients and a wide spectrum of DES substitution therapy medications (STMs) present on the national market [1, 2, 3], the treatment of this category of patients is predominantly empirical, without the consideration of the pathogenetic mechanism of disorder of the tear film renewal process. However, modern diagnostic tools allow to determine the pathogenetic mechanisms of DES development, particularly, to determine the layer (layers) of the tear film, the disorder of which caused the development of DES in this concrete patient. Based on this data, it is possible to make personalized selection of substitution therapy medications [5, 6, 9, 10].

Tear film is composed of three layers: mucin layer, aqueous layer and lipid layer, each of which performs certain functions [5, 10]. A thin mucin layer contacts with corneal epithelium and has a metabolic (ensures the delivery of nutrients to corneal epithelium as well as the removal of metabolites; facilitates corneal epithelium regeneration; ensures hydration of epithelial cells) as well as light-refracting functions (evens out the surface of the outer membrane of corneal epithelium; keeps the tear film on the outer membrane of the corneal epithelium and conjunctiva) [6, 10]. In addition to the functions described above the aqueous layer, which is the largest in volume, performs a protective function. The metabolic function of the aqueous layer lies in transport of oxygen, nutrients and a removal of metabolites, dead epithelial cells; in facilitation in corneal epithelium regeneration in ensuring the hydration of epithelial cells. The aqueous layer is the basis of the natural "contact lens" presented in the form of pre-corneal tear film, which ensures its light-refracting function. The protective function lies in the mechanical removal (washing off) of foreign bodies from the surface of corneal epithelial; in the anti-bacterial and anti-virus activity; in restoration of pH-level of the tear liquid in case when weak acids and/or alkali penetrate the conjunctival cavity [9, 10]. The lipid layer is external and has a protective (prevents various aerosols from penetrating the corneal epithelium, including the airborne infections pathogens; provides thermal isolation of the corneal epithelium and conjunctiva; decreases the evaporation of the aqueous layer) and light-refractory (evens the outer surface of the tear film) functions [5, 9, 10].

That is why the purpose of the study is to substantiate the personalized selection of substitution therapy medications with the consideration of the pathogenesis of DES development in each patient.

MATERIALS AND METHODS OF RESEARCH

In order to achieve the set goal, we conducted a content-analysis of the information on active ingredient from nomenclature as well as on the mechanisms of STMs action provided in the prescribing information and labeling of the medications. After that we performed a pathogenetic ranging of STMs depending on the way they influence a certain aspect of disorder of the tear film renewal process under DES.

RESULTS AND DISCUSSION

STMs' action in DES is determined by the presence of hyaluronic acid in their composition in the form of sodium hyaluronate (either in a clear form or in combination with propylene glycol and guar), carbopol, methyl cellulose derivatives (hypromelose and carmellose), polyquad, povidone, polyvinyl alcohol, dexpanthenol with taurine, trehalose, vitamin complex with amino acids, ectoin, Omega-3 [1-4, 8].

Hyaluronic acid has a chemical structure, molecular mass and rheological properties similar to a component of human tears, namely, mucin. Because of its properties, hyaluronic acid moistures the eye not affecting the vision. In addition, its ability to bind water allows to keep the ocular surface lubricated. When applied locally, hyaluronic acid increases the stability of the pre-corneal tear film, positively influences the epithelial layer, facilitates the increase in the tear liquid volume and corneal wetness, decreases tear evaporation from the ocular surface as well [3, 8]. Carbopol is a high-molecular carboxyvinyl polymer that increases the viscosity of the tear liquid. A drop of the medication creates a protective and moisturizing film on the cornea [3, 8]. Hypromelose is soluble in water and is a derivative of a natural polymer of cellulose. It has high viscosity, thus slowing down liquid outflow and increasing the period of its contact with the cornea. It is a protector of corneal epithelium, it improves tear film stability, increases the contact period between the cornea and other active ingredients. Hypromelose facilitates the regeneration, stability and renewal of optic characteristics of the tear film, stimulates the regeneration of the ocular mucous membrane, normalizes cell metabolism, speeds up mitosis and increases the strength of collagen fibers, facilitates the improvement of energy processes, stimulates reparative processes in dystrophic disorders, normalizes the processes, distortion of which is accompanied by a considerable changes in the metabolism of ocular tissues, moisturizes and preserves the physiological properties of the ocular mucous membrane in condition of tear liquid insufficiency due to a quick onset of action and a long-lasting effect [3, 8]. Poluquad (polyquaternium-1) is a high molecular polymeric compound (4,600 – 11,000 Dalton) with a high charge density, which tends to increase liquid viscosity, thus influencing the influencing the biological accessibility of the medication and without having a pharmacological effect [3, 8]. Physico-chemical properties of povidone ensure its lubricating effect and the ability to absorb on the ocular surface, to lower the surface tension and increase the viscosity of water solutions. Spreading on the surface of cornea and conjunctiva, povidone acts as mucin substitute and prevents the development of eye irritation and, consequently, corneal epithelium dehydration [3, 8]. Polyvinyl alcohol has properties similar to the properties of mucin (substances that are produced by ocular conjunctiva) [3, 8]. Taurine is a sulphonic acid that the body synthesizes from the cysteine amino acid and plays a significant role in the tissue regeneration process. Taurine helps to improve the energy processes, stimulates the reparative process in case of dystrophic disorders, normalizes the processes, the disorder of which is accompanied by a considerable change in ocular tissue metabolism [3, 8]. Trehalose is a disaccharide that has protective, lubricating, regeneration and anti-oxidant properties. It is a key factor of dehydration processes (slowing down metabolic processes in conditions of hydration deficiency), a natural osmoprotector and bio-protector [3, 8]. Ectoin is a natural cell protecting molecule, which has membrane- and lipid-stabilizing properties, lowers the level of inflammation caused by irritation or conjunctiva dryness, which are the key symptoms of the dry eye syndrome. It lubricates the ocular surface and prevents its further dehydration. It stabilizes the lipid layer of the tear film and protects ocular cells from hyperosmolarity. It facilitates the regeneration of the dry and irritated conjunctiva [3, 8].

As dry eye syndrome often causes the lipid layer thinning, the substitution of lipids with lipid containing tear substitutes and sprays is well grounded. That is why while choosing "artificial tear" for cases of increased evaporation of the tear film, one should first focus on medications which have a prosthetic effect on the lipid layer of the tear film, such as STMs containing omega-3 [3, 8]. Hydroxypropyl-guar attracts water and keeps it on the ocular surface, facilitating the even distribution of the STM drop on the ocular surface, covering the affected segments like a protective plaster [3, 8]. Dexpanthenol is a B_5 pro-vitamin, a derivative form and an

alcohol analogue of pantothenic acid. Dexpanthenol, which is a component of an STM, stimulates the regeneration of the mucous membrane of the ocular surface, normalizes cell metabolism, speeds up mitosis and increases the strength of collagen fibers. Thus it causes the regenerative, metabolic and a weak anti-inflammatory effect of the drops. After linking with coenzyme A, which is a co-factor of various reactions, catalyzed by ferments and accompanied by acetyl group migration, pantothenic acid acts as a vitamin [3, 8]. Propyleneglycol stabilizes the tear film, shortens its break-up time [3, 8].

In addition, STMs may contain a complex of vitamins, amino acids and phospholipids. Namely, vitamin A normalizes tissue metabolism, takes part in oxidation-reduction processes, synthesis of mucopolysaccharides, proteins and lipids, stimulates cell regeneration. Vitamin E is a natural anti-oxidant; it protects cell membranes from oxidation related changes. Phospholipids distribute themselves on the ocular surface and form a film, which duplicates the lipid layer, acts as a barrier, decreases the evaporation of the aqueous layer of the tear film [3, 8]. Vitamins A and E have a calming and softening effect and in combination with phospholipids provide functional support of the lipid component of the eyelids and stabilization of the lipid component of the tear film, which plays a crucial role in the protective function of the tear liquid and control of its evaporation [3, 8]. L-prolin is one of the most important components of the collagen protein – the basis of all human body tissues. It supports the normal state of the conjunctive tissues (sclera of the eye, vessels). L-glycine is a central inhibitory neurotransmitter, improves metabolic processes. L-lysine has an anti-inflammatory, anti-swelling and painkilling effect. L-leucine participates in protein synthesis, activates cell and humoral immune response, increases the function of phagocytes, activates the processes of biosynthesis of amino acids, their predecessors and metabolites, prevents metabolic disturbances, which occur under stress [3, 8].

Thus, generalizing the above mentioned information, we have sorted the STMs by their influence of the tear film layers (table).

Influence of the dry eye syndrome substitution therapy medications corresponding tear film layer

Name of the STM	Influence of the corresponding tear film layer		
	aqueous	mucin	lipid
SUPEROPTIC™ KOMLIT eye drops 10 ml vial No.1	+	+	+
LAKRISEK OFTA PLUS eye drops, 8 ml vial, sterile, No.1	+	-	+
SYSTEIN BALANS ZASIB DLIA ZVOLOZHENNIA OCHEY 10 ml, No.1	+	+	+
KRAPLI OCHNI AY-TI EKTOIN 0.5 ml ampulla, No.10	+	+	+
KRAPLI OCHNI AY-TI EKTOIN PRO 0.5 ml ampulla, No.10	+	+	+
KATIONORM KRAPLI OCHNI 10 ml emulsion, No.1	+	+	+
VIDISIK ocular gel 0.2%, 10 g in a tube; 1 tube in a card box	+	+	-
OFTAGEL'®, ocular gel, 2.5 mg/g, 10 g in a vial; 1 vial in a card box	+	+	-
OFTAGEL'® UNO ocular gel, 2.5 mg/g	+	+	-
SIKAPOS ocular gel, 2 mg/g, 10 g in a tube, 1 or 3 tubes in a box	+	+	-
SHTUCHNI SLIOZY eye drops, 5 ml, or 10 ml, or 15 ml in a "Drop-Tainer®" dropper vial; 1 dropper-vial in a box made of card	+	+	-

Table continuation

Name of the STM	Influence of the corresponding tear film layer		
	aqueous	mucin	lipid
TEALOZ® DUO ROZCHYN OFTALMOLOHICHNYI 10 ml vial, sterile, No.1	+	+	-
OPTINOL 0.21% or 0.4% eye drops 10 ml	+	+	-
OPTINOL® INTENSYV eye drops 10 ml No.1	+	+	-
SUPEROPTIK AKVA eye drops 5 ml vial, No.1, 2	+	+	-
AKVILA KRAPLI OCHNI eye drops 0.18 % polymer container 0.4 ml, sterile, No.10	+	+	-
OKUTIARZ eye drops 10 ml vial, No.1	+	+	-
OKUKHIL C KRAPLI OCHNI ZAKHYSNI solution 10 ml, No.1	+	+	-
ARTELAK® SPLESK POZCHYN ZVOLOZHUYUCHYI DLIA OCHEY I KONTAKTNYKH LINZ 0.24 % solution, 10 ml vial, No.1	+	+	-
KHILO-KOMOD eye drops 1 mg/ml, 10 ml in a multi-dose container, equipped with an air-tight pipe and closed with a cap, 1 container in a card box	+	+	-
KHILO-KOMOD FORTE eye drops, 2 mg/ml, 10 ml in a multi-dose container, equipped with an air-tight pipe and closed with a cap, 1 container in a card box	+	+	-
SYSTEIN ULTRA ZASIB DLIA ZVOLOZHENNIA OCHEY 10 ml vial. No.1, 0.7 ml container, No.30	+	+	-
ZASIB DLIA ZVOLOZHENNIA OCHEY SYSTEIN® gel solution 10 ml No.1	+	+	-
SYSTEIN AKVA ZASIB DLIA ZVOLOZHENNIA OCHEY 10 ml, No.1	+	+	-
ZASIB D/ZVOLOZHEN. OCHEY SYSTEIN 10 ml vial, No.1	+	+	-
OPTIVE® eye drops in 3 ml, 10 ml, 15 ml dropper vials No.1	+	+	-
VIAL'® SLIOZA drops 10 ml polyethylene vial, No.1	+	+	-
HIPROMELOZA-P, eye drops 0.5%, 10 ml dropper-container, No.1	+	+	-
UNITIRS eye drops 10 ml vial, No.1	+	+	-
ARTELAK® eye drops, solution, 3.2 ml/mg 10 ml in a vial with a dropper; 1 vial with a dropper in a box	+	+	-
VIZILOTON ZASIB OFTALMOLOHICHNYI 10 ml, No,1	+	+	-
OFTOLIK eye drops, 5 ml or 10 ml in a plastic dropper-vial; 1 dropper-vial in a card box	+	+	-
VET-KOMOD eye drops, 20 mg/ml 10 ml in a multi-dose plastic container, equipped with an air-tight pipe; 1 container in a card box	+	+	-
KHILO®-KEA eye drops 10 ml multi-dose container with a pipe and a cap, No.1	+	-	-

CONCLUSIONS

The information received in the course of the conducted research makes it possible for an ophthalmologist to prescribe targeted DES treatment taking into account the necessary point of application of the substitution therapy medications considering their composition and mechanism of action of the active ingredients which they contain basing on the information on the distortion in the quantitative and qualitative correlation between the tear film layers receeved with the help of modern diagnostic tools.

Conflict of interests. The authors declare no conflict of interest.

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