Romanian Journal of Ophthalmology, Volume 60, Issue 3, July-September 2016. pp:153-157

REVIEW

Ocular surface - a complex and vulnerable adoptive environment for topical glaucoma treatment

Potop Vasile
"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

Correspondence to: Vasile Potop, MD, Associate Professor of Ophthalmology,
"Carol Davila" University of Medicine and Pharmacy,
8 Eroii Sanitari Blvd., Code 050474, District 5, Bucharest,
E-mail: potopvasile@yahoo.com

Accepted: July 15, 2016

Abstract

Ocular surface is a complex functional unit in which tissues so different as structure and function harmonize to produce a very short life (15-45 sec) film - tear film essential for the quality of the vision.

With age, the ocular surface undergoes a physiological decline, often with a limitation of its functionality.

Administration of topical glaucoma treatment itself constitutes a solicitation of the ocular surface and the nature of "accessories" included in this "drop glaucoma treatment", that might be the last straw which breaks the fragile balance or aggravates a previously nonexistent suffering subclinical symptomatology by opening and inducing reactions to treatment. Topical treatment in glaucoma could have the complex aspect of an adoption.

Every adoption is a delicate and unpredictable phenomenon.

Success does mean harmony and coexistence. For the adoption to succeed, one needs to know well the adoptive environment, the adopted element and the science and art to harmonize them together.

Keywords: ocular surface, topical glaucoma treatment, tear film

Introduction

Topical treatment in glaucoma has a lifelong administration, often gradually increasing the number of administered substances. A prolonged administration of such a treatment appears as a true act of adoptions, the ocular surface being an adoptive environment. Moreover, the topical glaucoma treatment is an adopted element, which harmonizes the two factors that provide treatment tolerance and success thereof.

For a relationship to succeed, the adoption must know the foster, the adopted and then find the way to harmonize them.

Adoptive environment

The ocular surface is a complex and dynamic adoptive environment, which is equally vulnerable.

It is almost a miracle that so different ocular tissues from the anatomical and functional (conjunctiva and cornea) point of view are anatomically delimited so net, but are complex when harmonizing through a fluid (tear film) into a functional unit, called the ocular surface. The tear film is a very short live film (15-40 seconds), which opens the way to visual perception.

The structure of the tear film

The external lipid layer has a thickness of 0.1 microns. It is produced by Meibomius, Zeiss and Moll glands. Moreover, it contains low polar lipids (cholesterol esters), highly polar lipids (TG, fatty acids, phospholipids) and has the role of preventing the evaporation of the tear film and tears overflow.

The aqueous layer is produced by the main lacrimal gland and accessory glands Krause and Wolfring. It is the main component of the tear film, having a thickness of 7-8 microns over the cornea.

It provides oxygen to the corneal epithelium, removes debris and contains antibacterial substances, lysozyme, betalizine, etc.

The inner layer of mucin is produced by the conjunctival goblet cells and squamous epithelial cells of the conjunctiva and cornea and has a thickness of 0.2 microns.

It has a vital role in the stability of the tear film hydrophobia, converting the hydrophilic corneal epithelium. It lubricates the ocular surface and eyelid and forms a sheath around foreign bodies, protecting them from their abrasive effect over the cornea.

Foster environmental dynamics

Blinking is dispersed all over the corneal tear film [**1**]. After 15-45 sec., the film breaks and breakpoints occur (dry spots).

The drying of the corneal surface might not be only the result of evaporation (evaporation should take 10 minutes to dry the cornea).

Holly – Lemp Mechanism [**2**] presupposes that the tear film thins gradually, first by evaporation.

When the thickness reaches a critical level, some lipid molecules adhere to the mucin layer and interfere with it.

Once the mucin layer is mixed with more fat, it becomes hydrophobic and the tear film breaks.

Holly described the dynamics of the tear film during blinking in 1980.

During blinking, the upper eyelid downs to compress the lipid layer surface between the edges of the eyelids. The lipids are mixed with the palpebral mucus. This way, thread-like mixtures that reach the inferior fornix are formed.

When open, the eye lipids disperse in a single layer by the action of the upper eyelid. Lipids in excess disperse and the second lipid layer forms in one second. In their dispersion, lipids draw tears and thicken the aqueous tear film.

Foster environmental assessment

Regarding the examination of the tears film [**3**], the breaking time of the tear film (BUT) correlates with the ocular index. It is the ratio between BUT and the interval between two successive blinks. When the latter exceeds BUT, the same corneal areas remain dry and may induce symptoms of dryness. The stability test of the tear film-BUT – proves abnormal in 10 seconds

The tear volume (Schirmer) test is considered abnormal when, after 5 minutes, <10 mm without anesthesia or < 5 mm with anesthesia.

Tear osmolarity [**4**] values of over 316 mOsm proved relevant for the ocular surface examination (staining).

Sodium fluorescein examination, used during the BUT color areas, in which there is a rupture of intercellular connections, allows the access of stain.

Rose Bengal stain examination stains the cell zones, which suffer after having lost mucus coating.

Lissamine Green is used to grade the damage of the conjunctiva.

Sensitive or suffering adoptive environment

The adoptive environment can often have a chronic condition before adopting the topical glaucoma treatment. It is a multifactorial disease of the ocular surface and lacrimal system with symptoms like dry eye [**3**], quantitative and qualitative impairment of the tear film, tear film instability, blurred vision, dryness, associated with damage to the ocular surface.

Disorders of lipid - layer chronic blepharitis

Aqueous - deficient KCS, idiopathic systemic diseases

Deficit of mucin - hypovitaminosis, ocular cicatricial pemphigoid, Stevens-Johnson induced by burns

Eyelid function disorder, exposure keratitis, symblepharon, pterygium

Epitheliopathy - anesthetic cornea, epithelial irregularity

In such cases, the adoption of a topical glaucoma treatment may exceed the functional availability of the ocular surface and the other alternative treatment modalities (surgery, laser) should be taken into account. Otherwise, topical treatment may exacerbate the existing symptoms and pathology, the patient's compliance decreasing.

This is the unfortunate situation, in which the topical treatment of glaucoma does not meet the adoptive environment conditions. Therefore, the topical treatment of glaucoma should be changed with laser or surgery.

The treatment/ adoption

The topical drops in the treatment of glaucoma contain an active substance and various accessories [**5**], which help in correcting the pH, osmolarity, sterility, etc., of the solution.

Both active components and accessories can induce changes in a normal ocular surface and, its disturbing, may lead to its poor functionality, or may aggravate a prior suffering. The chronic administration of substances regardless of their nature, challenge the functions of the ocular surface. The effects on the ocular surface may be determined by the active substance contained therein, or preservatives and the degree of damage is related to the nature of the preservative, the number of administrations and the number of drugs used.

Preservatives are substances that prevent the development of bacterial germs by acting on their direct cytotoxic effect or by lysis of the cell membrane to the cytoplasm lost.

There are two classes of preservatives: detergents and oxidizers.

Table 1. Classes of preservatives

Detergents	Oxidizers
Benzalkonium chloride (BAK)	Stabilized oxychloro complex (SOC/ purity)
Polyquaternium -1 (Polyquad)	Sodium perborate (GenAqua) Sofzia

Detergent preservatives act as surfactants that alter the cell membrane permeability resulting in lipid dispersion (tear film destabilization) [**5**] and lysis of the cytoplasmic contents.

Benzalkonium chloride (BAK or BAC) [**6**] is the most often used preservative in glaucoma drops and in over 70% of the glaucoma solutions bottles. The concentrations of 1/ 10 can cause cell necrosis and 1/ 100-1/ 10000 concentrations can cause apoptosis of goblet cells, or endothelial trabecular cells [**6-9**].

Oxidant preservatives penetrate the cell membrane and affect cellular functions by altering microbial lipids, proteins and DNA. Their action to destabilize the membrane is lower than that of detergents [**11**]. Animal and human studies have indicated that the preservatives can induce inflammation affecting the ocular surface [**10-12**].

Sometimes, the active substance may have a toxic effect; topical carbonic anhydrase inhibitors may affect corneal endothelium [**13,14**]. Epidemiological studies have shown that drops without preservatives caused fewer symptoms and signs of the ocular surface [**15-17**]. Topically treated ocular surface is affected in a large proportion of patients with glaucoma [**18,19**].

How can the topical treatment of glaucoma influence the ocular surface?

The topical treatment of glaucoma can affect the ocular surface with the appearance of symptoms and signs [**20**]: dryness, tearing, burning, foreign body sensation, photophobia, or visual impairment. Superficial punctate keratitis, allergic manifestations, or tear film instability may appear in the cornea and conjunctiva.

Superficial punctate keratitis occurs frequently after the topical administration of prostaglandins, beta-blockers, or pilocarpine, and is more frequent in preparations with preservatives [**25**].

The manifestations of allergic reactions are of type I, mediated by Ig E or type IV. They are induced by the active substance or preservatives and they manifest through burning, chemosis, conjunctival hyperemia or eyelid edema [**21,22**].

The tear film instability [**23,24**] is the most frequent effect of topical glaucoma therapy. It may be objectified by the BUT, Schirmer's test, tear osmolarity, or exam of the Meibomius glands.

The effect of the ocular surface due to topical glaucoma therapy may affect the treatment compliance and thus decrease the tolerance to the treatment. The asymptomatic disease glaucoma can become a disease with symptoms of dry eye. The adoptive environment cannot tolerate the adopted element.

How to treat glaucoma, sparing the ocular surface

There are no templates to adapt topical glaucoma therapy to the suffering ocular surface. There are only individual cases and even asymmetry between the two eyes in the same patient.

The adequacy of treatment for the ocular surface evaluation of the deficits and their compensation is the following: lubricants, short-term corticosteroid administration. Allergic reactions may require a discontinuation for short-term or the drops replacing and toxicity would indicate the use of single-dose preparations or without preservatives.

The selection of the topical treatment of glaucoma is performed according to the dosage and their toxicity to the ocular surface (less preservatives [**26,27**], reduced dosage). At the same time, a prolonged treatment with preparations containing high concentrations (< 1/1000) BAK certainly causes a severe damage to the ocular surface [**28-30**].

Taking into account the topical glaucoma treatment symptoms, the ocular surface symptoms of distress in these patients can be the only ocular symptoms, the patient being able to overstate them avoiding treatment.

Moreover, there may be symptoms without an objective support, which can be objectified as deficits without symptoms.

In chronic glaucoma, the constant risk factor is age, the ocular surface undergoing a sharp decline with age. Under these conditions, any prolonged topical therapy is a strength test.

A periodic evaluation of the ocular surface would pinpoint its suffering, before symptoms turn glaucoma from an asymptomatic disease into a troublesome one.

Every adoption is a complex act, whose purpose depends on the baseline (foster environmental awareness, the correct choice of the adopted) and continuous harmonization relationship between the two factors.

The topical therapy of glaucoma may be viewed as a special adoption. Therefore, the question which arises is the following: "Who would grant an adoption of a deficits elder family with multiple vulnerabilities especially when one adopted is liable of creating problems even though foster (ocular surface) is a normal environment?".

The ocular surface is instead a sublime harmony. In addition, topical therapy of glaucoma is the science of integrating certain topical glaucoma treatment in this harmony and maintaining it.

References

1. Tsubota K. Tear dynamics and dry eye. Prog Retin Eye Res. 1998; 17:565-9.
2. Holly FJ, Lemp MA. Tear physiology and dry eyes. Surv Ophthalmol. 1977; 22:69-87.
3. Definition and Classification Subcommittee of the International Dry Eye Work Shop. The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye Work Shop (2007). Ocul Surf. 2007; 5:75–92.
4. Lemp MA, Bron AJ, Baudouin C et al. Tear osmolarity in the diagnosis and management of dry eye disease. Am J Ophthalmol. 2011; 151:792–798.
5. Tressler CS, Beatty R, Lemp MA. Preservative use in topical glaucoma medications. Ocul Surf. 2011; 9:140–158.
6. Ye J, Wu H, Zhang H et al. Role of benzalkonium chloride in DNA strand breaks in human corneal epithelial cells. Graefes Arch Clin Exp Opthtalmol. 2011; 249;1681-1687.
7. Ammar DA, Noecker RJ, Kahook MY. Effects of benzalkonium chloride and polyquad-preserved combination glaucoma medications on cultured human surface cells. Adv Ther. 2011; 28:501–510.
8. Ammar DA, Kahook MY. Effects of glaucoma medications and preservatives on cultured human trabecular meshwork and nonpigmented ciliary

epithelial cell lines. Br J Ophthalmol. 2011; 95:1466–1469.
9. Ammar DA, Kahook MY. Effects of benzalkonium chloride-or polyquad-preserved fixed combination glaucoma medications on human trabecular meshwork cells. Mol Vis. 2011; 17:1806–1813.
10. Paimela T, Ryhanen T, Kauppinen A et al. The preservative polyquaternium-1 increases cytoxicity and NF-kappaB linked inflammation in human corneal epithelial cells. Mol Vis. 2012; 18:1189–1196.
11. Ayaki M, Iwasawa A, Inoue Y. Toxicity of antiglaucoma drugs with and without benzalkonium chloride to cultured human corneal endothelial cells. Clin Ophthalmol. 2010; 4:1217–1222.
12. Arici MK, Arici DS, Topalkara A, Guler C. Adverse effects of topical antiglaucoma drugs on the ocular surface. Clin Experiment Ophthalmol. 2000; 28:113–117.
13. Domingo Gordo B, Urcelay Segura JL, Conejero Arroyo J et al. Corneal decompensation in patients with endothelial compromise treated with topical dorzolamide. Arch Soc Esp Oftalmol. 2002; 77:139–144.
14. Konowal A, Morrison JC, Brown SV et al. Irreversible corneal decompensation in patients treated with topical dorzolamide. Am J Ophthalmol. 1999; 127:403–406.
15. Pisella PJ, Pouliquen P, Baudouin C. Prevalence of ocular symptoms and sings with preserved and preservative free glaucoma medication. Br J Ophthalmol. 2002; 86; 418-423.
16. Jaenen N, Baudouin C, Pouliquen P et al. Ocular symptoms and signs with preserved and preservative-free glaucoma medications. Eur J Ophthalmol. 2007; 17:341–349.
17. Baudouin C, Labbe A, Liang H et al. Preservatives in eyedrops: the good, the bad and the ugly. Prog Retin Eye Res. 2010; 29:312–334.
18. Leung EW, Madeiros FA, Weinreb RN. Prevalence of ocular surface disease in glaucoma patients. J. Glaucoma. 2008; 17;350-355.
19. Fechtner RD, Godfrey DG, Budenz D et al. Prevalence of ocular surface complaints in patients with glaucoma using topical intraocular pressure lowering medications. Cornea. 2010; 29:618–621.
20. Servat JJ, Bernadino CR. Effects of common topical antiglaucoma medication on ocular surface, eyelids, and periorbital tissue. Drug Aging. 2011; 28;267-282.
21. Badouin C. Allergic reactions to topical eyedrops. Curr Opin Allergy Clin Immunol. 2005; 5;459-463.
22. Hong J, Bielory L. Allergy to ophthalmic preservatives. Curr Opin Allergy Clin Immunol. 2009; 9;447-453.
23. Mantelli F, Tranchina L, Lambiase A, Bonini S. Ocular surface damage by ophthalmic compounds. Curr Opin Allergy Clin Immunol. 2011; 11;464-470.
24. Terai N, Muller-Holz M, Spoerl E, Pillunat LE. Short-term effect of topical antiglaucoma medication on tear-film stability, tear secretion and corneal sensitivity in healthy subjects. Clin Ophthalmol. 2011; 5;517-525.
25. Inoue K, Okugawa K, Kato S et al. Ocular factors relevant to antiglaucomatous eyedrop-related keratoepitheliopathy. J Glaucoma. 2003; 12:480–485.
26. Gandolfi S, Paredes T, Goldberg I et al. Comparison of a travoprost BAK-free formulation preserved with polyquaternium-1 with BAK-preserved travoprost in ocular hypertension or open-angle glaucoma. Eur J Ophthalmol. 2012; 22:34–44.
27. Kitazawa Y, Smith P, Sasaki N et al. Travoprost 0.004%/timolol 0.5%-fixed combination with and without benzalkonium chloride: a prospective, randomized, doubled-masked comparison of safety and efficacy. Eye. 2011; 25:1161–1169.
28. Uusitalo H, Chen E, Pfeiffer N et al. Switching from a preserved to a preservative-free prostaglandin preparation in topical glaucoma medication. Acta Ophthalmol. 2010; 88:329–336.
29. Renieri G, Fuhrer K, Scheithe K et al. Efficacy and tolerability of preservative-free eye drops containing a fixed combination of dorzolamide and timolol in glaucoma patients. J Ocul Pharmacol Ther. 2010; 26:597–603.
30. Katz G, Springs CL, Craven ER, Montecchi-Palmer M. Ocular surface disease in patients with glaucoma or ocular hypertension treated with either BAK-preserved latanoprost or BAK-free travoprost. Clin Ophthalmol. 2010; 4:1253–1261.